Cyclisation reactions for the synthesis of natural and unnatural piperidines

Barat, Viktor

2017

Barat, V. (2017). Cyclisation reactions for the synthesis of natural and unnatural piperidines.
Doctoral thesis, Nanyang Technological University, Singapore.

<http://hdl.handle.net/10356/72882>

<https://doi.org/10.32657/10356/72882>

NANYANG
TECHNOLOGICAL
UNIVERSITY

PhD Dissertation

Cyclisation Reactions for the Synthesis of Natural and
Unnatural Piperidines

BARÁT Viktor

Division of Chemistry and Biological Chemistry

School of Physical and Mathematical Sciences

2017

Cyclisation Reactions for the Synthesis of Natural and Unnatural Piperidines

BARÁT Viktor

School of Physical and Mathematical Sciences

Division of Chemistry and Biological Chemistry

A thesis submitted to the Nanyang Technological University in partial fulfilment
of the requirements for the degree of Doctor of Philosophy

2017

School of Physical and Mathematical Sciences
Nanyang Technological University

Plagiarism Declaration

I certify that this essay/report/assignment/thesis/dissertation titled

CYCLISATION REACTIONS FOR THE SYNTHESIS OF NATURAL AND UNNATURAL PIPERIDINES

Submitted on 18 / 08 / 2017 (DD/MM/YY) was written by myself and conforms to the NTU University Honor Code. I also further confirm that the following is true.

1. I understand what plagiarism entails and am aware of the University's policy in this regard. I am also aware that any cases of plagiarism detected will lead to suspension from the university and/or withdrawal of an awarded degree.
2. All experimental data/simulation results/calculations included have been presented without any bias, modifications or alterations, and can be obtained by others using the information provided in the report.
3. None of the material presented has been copied from published/unpublished sources (reports, textbooks, journal articles, magazines, online resources etc). Where material from any such source was copied, it has been put in quotation marks and the source was given due credit by citing it in the text at the appropriate location\locations and giving its full details in the section on references.
4. Where material (data/schemes/figures/tables etc) from any source was used, the source was given due credit by citing it in the text of the report at the relevant location\locations and giving its full details in the section on references.

Copyright and Permissions to use Agreement

I would like to declare that the following chapters are reproduced from **MY OWN PUBLISHED ARTICLES** and I hereby attached the Copyright and Permissions to use Agreement.

BARAT VIKTOR

Name

Signature

Acknowledgement

I would like to express my sincerest gratitude to my supervisor Associate Professor Roderick W. Bates for his endless guidance and support throughout my PhD journey.

A tremendous amount of help and support was given to me by former colleagues Siva, Filza and Tee Guan which was essential, and I am eternally thankful for that.

Completing this journey would have been impossible without the constant support and encouragement of my fellow grad students and countrymen in Singapore: Daniel, Gabor, David, and Laszlo.

I would like to thank the current and former members of the Bates group Lucia, Nisha, KC, Ivan, Weiting, Anders, Annabell, Padmakar, Vasu, undergrads, and exchange students for the stimulating environment.

My gratitude goes to the support and admin staff of CBC: Ms. Seow Ai Hua, Ms. Goh Ee Ling, Derek Ong, Dr. Rakesh Ganguly and Dr. Li Yongxin and the CBC Research & Graduate Office staff.

I am grateful to the people who made my stay in Singapore memorable and supported me throughout: Paola, Adam, Meshal, Ali, Biswa, Sumi, Blaz, Simin, Yorick, Karina, and Yen-Lyng.

Special thanks to the American Dragons Singapore and the International Dragon Boat Community for showing me a new experience that complements the difficulties of PhD life.

Lastly, I would like to thank my family and friends from Hungary for their love, support and patience during my time away from home.

Table of Contents

1. Platinum Catalysed Ring Opening Isomerisation of Piperidine Cyclopropanes	16
1.1 Abstract.....	17
1.2 Objectives	18
1.3 Ring Opening Reactions of Cyclopropanes: Literature Review	19
1.4 Ring Opening Reactions of Cyclopropanes: Results and Discussion	28
1.5 Rediscovery of the Prins Reaction.....	47
1.6 Prins Reaction: Literature Review	49
1.7 Prins Reaction: Results and Discussion	51
1.8 Conclusion and Summary.....	57
1.9 Experimental and Methods.....	58
1.10 References	75
 2. The Total Synthesis of Lupin Alkaloids	 79
2.1 Abstract.....	80
2.2 Introduction	81
2.3 Isolation and Biological Activity.....	81
2.4 Total Synthesis of Lupin Alkaloids: Literature Review	83
2.5 Follow-up on the Prins Reaction	89
2.6 Attempted Total synthesis of Lupin Alkaloids:.....	97

2.6.1 Total synthesis of Lupin Alkaloids: Epoxide Ring Opening	97
2.6.2 Total synthesis of Lupin Alkaloids: Tsuji-Trost Reaction	103
2.6.3 Total synthesis of Lupin Alkaloids: Vinyl Iodide Coupling	107
2.6.4 Total synthesis of Lupin Alkaloids: Masked buta-1,3-diene	109
2.6.5 Total synthesis of Lupin Alkaloids: 6-endo-dig Cyclisation	110
2.7 Total synthesis of Lupin Alkaloids: 6-endo aza-Michael Cyclisation	117
2.7.1 Aza-Michael Cyclisation in Total Syntheses	119
2.7.2 Total Synthesis of rac-Cytisine	123
2.7.2.1 Synthesis of the Cyclisation Precursor	124
2.7.2.2 Optimisation of the aza-Michael Cyclisation	128
2.7.2.3 Identifying the Individual Diastereoisomers	130
2.7.2.4 Synthesis of Racemic Cytisine	133
2.7.3 Studies towards Further Lupin alkaloids	138
2.7.4 Enantioselective Total Synthesis of Lupin alkaloids	149
2.8 Conclusions and Summary	167
2.9 Future work	168
2.10 Experimental and Methods	171
2.11 References	194

Summary

When it comes to the synthesis of substituted heterocycles, cyclisation reactions have a great potential alongside the functionalisation of cyclic molecules as stereochemistry can be controlled through the transition states by careful substrate design and the appropriate choice of reaction conditions. The synthesis of piperidines and piperidine containing natural products was achieved through various cyclisation reactions with a strong focus on steric control.

A series of *N*-tosyl homoallylamines were cyclised using a hydroformylation/intramolecular condensation cascade to yield cyclic ene-sulfonamides which were subsequently cyclopropanated in a diastereoselective fashion. Mechanistic studies on the ring opening reactions of these piperidine cyclopropanes using Pt(II) catalysts furnished *endo* and *exo*-cyclic olefin products which were further cyclopropanated again with complete control of stereochemistry. When attempting to ring open this new type of piperidine cyclopropanes, a Pt(II) driven Wagner-Meerwein type 1-2-alkyl shift reaction was observed which was never reported before, to the best of our knowledge.

During the cyclopropanation study, a new and mild version of the Prins reaction was discovered which furnished a never before reported bicyclic piperidino-dioxane scaffold. This interesting compound turned out to be surrogate for hydroxymethyl-piperidines which inspired the total synthesis of some Lupin alkaloids. Although this approach was proven unsuccessful, the Lupin alkaloids were attempted to be prepared using a range of cyclisation reactions yielding carbo and heterocycles.

The total synthesis of (-)-*cytisine* was achieved using a 6-*endo aza*-Michael reaction, and the developed approach can yield three more Lupin natural products in a stereodivergent fashion, and the prospect to extend this methodology for the synthesis of quinolizine alkaloids in the Lupin family.

List of abbreviations

))) : sonication

Ac: acetyl

anh: anhydrous

aq: aqueous

BIPHEPHOS: 6,6'-[(3,3'-Di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl- 2,2'-diyl)

bis(oxy)]bis(dibenzo[d,f][1,3,2]dioxaphosphepin)

Bn: benzyl

^tBu: *tert*-butyl

Bz: benzoyl

Cbz benzyloxycarbonyl

CDI: carbonyldiimidazole

COSY: Correlation spectroscopy (NMR)

CyJohnPhos: (2-Biphenyl)dicyclohexylphosphine

Dbz: dibenzalacetone

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC: dicyclohexylcarbodiimide

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEAD: diethyl azodicarboxylate

DIPEA: N,N-diisopropylethylamine

DMAP: 4-(dimethylamino)pyridine

DME: 1,2-dimethoxyethane

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

dr: diastereomer ratio

DTAD: di-*tert*-butyl azodicarboxylate

d: doublet

EDCI: 1-ethyl-3-(3-diaminopropyl)carbodiimide

ee: enantiomer excess

ent: enantiomeric

Et: ethyl

EWG: electron withdrawing group

HMDS: bis(trimethylsilyl)amine / bis(trimethylsilyl)amide (anion)

HMPA: hexamethylphosphoramide

HOBt: 1-hydroxybenzotriazole

h: hour(s)

IBX: 2-iodoxybenzoic acid

IR: infra-red spectroscopy

J: coupling constant

LA: Lewis acid

LDA: lithium diisopropylamide

Me: methyl

m: multiplet

MS: mass spectrometry

Ms: methanesulfonyl

MOM: methoxymethyl

NBS: *N*-bromo succinimide

NOESY: Nuclear Overhauser effect spectroscopy (NMR)

NMR: nuclear magnetic resonance spectroscopy

Ns: (nosyl) : 2-nitrobenzenesulphonyl group

Nu: nucleophile

Ph: phenyl

ⁱPr: isopropyl

1,10-phen: 1,10-phenantroline

Piv: pivaloyl (group)

pTSA: p-toluenesulfonic acid

Pyr: pyridine; pyridyl (group)

q: quartet

rt: room temperature

s: singlet

sat: saturated

SM: starting material

t: triplet

TBAB: tetra-n-butylammonium bromide

TBAF: tetra-n-butylammonium fluoride

TBS tert-butyldimethylsilyl

Tf: trifluoromethanesulfonyl (triflyl)

TFA: trifluoroacetic acid

TFE: 2,2,2-trifluoroethanol

TLC: thin layer chromatography

TMANO: trimethylamine *N*-oxide

TMEDA: N,N,N',N'-tetramethyl- 1,2-ethylenediamine

TMG: 1,1,3,3-tetramethylguanidine

TMS: trimethylsilyl

Ts: tosyl, 4-toluenesulfonyl

Chapter 1

Platinum Catalysed Ring Opening

Isomerisation of Piperidine

Cyclopropanes

1.1 Abstract

We report the platinum mediated ring opening isomerisation of piperidine cyclopropanes. Such transformations of these compounds were never studied before to the best of our knowledge.

We have synthesized a library of piperidine cyclopropanes which undergo ring opening isomerisation when treated with Pt(II) catalysts yielding either an *endo* or an *exocyclic* olefinic product. The proposed mechanism of the transformation involves C-C bond activation and β -hydride elimination. In case of substrates without any β -hydrogen, a platinum-mediated Wagner-Meerwein alkyl shift is observed with complete diastereoselectivity.

An interesting side reaction was investigated and led us to discover a new approach to the Prins reaction under extremely mild conditions. Moreover, Prins reactions of *N*-substituted alkenes have obtained very little attention in the past and this will be the second report of such a reaction.

Functionalization of ene-sulfonamides

1.2 Objectives

- Synthesis of a piperidine cyclopropane library using literature examples and *in-house* procedures.
- Proving the stereochemical outcome of the cyclopropanation reaction of α -substituted cyclic ene-sulfonamides which was postulated in the literature without evidence.
- Investigating the scope and limitations of the cyclopropane ring opening reaction with particular focus on functional group tolerance.
- Investigating the reaction of the postulated iminium ion intermediate with intra- and intermolecular nucleophiles.
- Synthesis and ring opening of piperidine cyclopropanes without β -hydrogen and the study of ring opening mechanism.

1.3 Ring Opening Reactions of Cyclopropanes: Literature Review

Cyclopropanes exhibit unusual reactivity amongst cycloalkanes, due to their bond angle which is far from the thermodynamically favoured tetrahedral angle of 109.5° . This causes ring strain known as Baeyer-strain, and angle strain as well, since the molecule is not flexible. The ring strain of cyclopropane is 27.5 kcal/mol, which is the highest amongst cycloalkanes (cyclobutane 26.3 kcal/mol, cyclopentane 6.2 kcal/mol, cyclohexane 0.1 kcal/mol, cycloheptane 6.2 kcal/mol).¹

The carbon-carbon bonds of cyclopropane have a short length (1.52 Å), but a low dissociation energy (57 kcal/mol).² These C-C bonds show a partial π -character and the C-H bonds of cyclopropane are similar to those in ethylene.

Cyclopropane was discovered in 1881 by August Freund.³ He proposed its structure based on the reactions of cyclopropane with bromine and hydrogen iodide. The structure proposal was correct and in fact he discovered the first cyclopropane ring opening reactions as well.

The first cyclopropane derivatives⁴ were synthesized at the late 19th century and they were proven to be stable as well (Figure 1).

Figure 1: Early synthesis of cyclopropane derivatives by Perkin

The question of stability arose from a scientific debate between Perkin and Fetter, where Fetter was trying to prove that **1-1** does not contain a cyclopropyl moiety, but was in fact diethyl vinylmalonate. He was proven wrong when Franchimont showed that **1-1** is a disubstituted malonate.⁴

The first catalytic hydrogenolysis of cyclopropanes was achieved in 1907 by Willstätter and Bruce with a nickel catalyst.⁵ Several other heterogeneous methods were discovered using

metals and metal oxides in the following years and this reaction was a popular area of kinetic studies as well.²

Ring opening of cyclopropanes can be achieved through several approaches⁶. Acidic conditions were utilized during the total synthesis of ($\pm$)-goniomitine⁷ and for some calcimycin class antibiotics⁸ (Figure 2), as well as crinosterol and brassicasterol.⁹ This type of transformation has been used in total synthesis as we can see from the examples below.

The ring opening of electron-poor cyclopropanes with nucleophiles was described by Danishefsky.¹⁰ Their activated cyclopropane **1-2** underwent homoconjugate additions showing similar reactivity as olefins in Michael additions (Figure 2).

Figure 2: Ring opening of an activated cyclopropane by Danishefsky

Captodative cyclopropanes show facile ring opening when prepared *in situ*.¹¹ These compounds bearing electron-donating and accepting groups can ring open spontaneously (Figure 3).

Figure 3: *In situ* ring opening of a captodative cyclopropane

Another approach for the ring opening of cyclopropanes is the reaction with electrophiles. Cyclopropanes react similarly to olefins, usually following Markovnikov's rule in case of substituted cyclopropanes.⁶ The ring openings of 2,3-cyclopropanated sugars with halonium

ions¹² were performed by Nagarajan (Figure 4). Also, salts of mercury¹³, silver¹⁴ and ytterbium¹⁵ can be used for ring openings as electrophiles.

Figure 4: Cyclopropane ring opening with mercury salts by Nagarajan

The ring opening of cyclopropanated piperidines was investigated by Harrity.¹⁶ Besides the brominative ring opening, he has trapped the iminium ion intermediate with an intramolecular nucleophile (Figure 5).

Figure 5: Ring opening with iminium ion trapping by Harrity

The acid-mediated diastereoselective ring opening of 2,3-cyclopropanated sugars was investigated by Hoberg and Claffey¹⁷ (Figure 6). Also, a method was developed for the ring opening of these cyclopropanes resulting in the ring expansion to the 7-membered oxepanes¹⁸ using TMSOTf.

Figure 6: Acidic ring opening of cyclopropanated sugars by Hoberg

The most important approach for us is the transition metal mediated ring opening of cyclopropanes. Gaasbeek reported the first iridium complex for ring opening of a cyclopropane in 1969.¹⁹ They used $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ (Vaska's complex) to obtain an exocyclic olefin (**1-16**)

from a cyclopropanated norbornadiene (**1-15**). They also isomerized a double bond²⁰ in the cyclohexene substrate using $\text{Rh}_2(\text{CO})_4\text{Cl}_2$ as a catalyst precursor (Figure 7).

Figure 7: Transition metal mediated isomerization of cyclopropanes using Ir and Rh

Activated vinylcyclopropanes can be ring opened and used in cyclisation reactions. The ring opening can be achieved with palladium²¹ and nickel²² complexes (Figure 8).

Figure 8: Ring opening and cross coupling of activated vinylcyclopropanes

The carbonylative ring opening of cyclopropane substituted amides has been used to synthesise fused heterocycles.²³ This chemistry involves the Rh mediated ring opening of the cyclopropane ring, carbonylation, and an intramolecular nucleophilic attack to achieve ring closure (Figure 9).

Figure 9: Carbonylative cyclopropane ring opening

The most important achievements in this field were attributed to platinum catalysed reactions. Cyclopropane complexes of platinum were investigated by Tipper²⁴ who reported these compounds to be stable, indicating a strong coordination to the metal. He investigated the

stability of several complexes and he only managed to remove cyclopropane from the coordination sphere of the platinum under harsh conditions. Of course, at that time, it was not known that these compounds exist as platinacyclobutanes.²⁵

Beyer and Madsen²⁶ investigated the platinum catalysed ring opening reactions of cyclopropanated sugars and tetrahydropyrans. They treated 1,2-cyclopropanated tetrahydropyran (**1-22**) with $[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$, commonly known as Zeise's dimer, to yield the corresponding exocyclic olefin (**1-23**) (Figure 10).

Figure 10: Pt mediated ring opening of a cyclopropane by Madsen

The platinum catalysed rearrangement of alkoxy substituted cyclopropanes²⁷ was known. They intended to subject a cyclopropanated sugar (**1-24**) to the same transformation but the product was not the desired one. They obtained the benzyl glycoside (**1-26**) of the original cyclopropanated sugar. This led them to a mechanistic discovery and they proposed a mechanism for this reaction (Figure 11).

Figure 11: Ring opening of cyclopropanated sugar via platinacyclobutane intermediate

Madsen presumed that BnOH reacted with one of the intermediates. It was known that cyclopropanes react with platinum compounds to form stable platinacyclobutanes (**1-27**).²⁵ The Pt-C bond was assumed to be polarized by the electron donation of the oxygen, and the

nucleophilic attack of benzyl alcohol on the resulting oxocarbenium ion (**1-28**) followed by the reductive elimination of Pt(II) yielded the benzyl glycosylate (**1-26**) (Figure 12).

Figure 12: Proposed mechanism for the ring opening by Madsen

Madsen continued the studies towards the ring openings and this led to the discovery that electrophilic palladium complexes provide a Ferrier-type rearrangement to yield 2,3 unsaturated glycosides (**1-35**).²⁸ The mechanism of this reaction is fundamentally different than the previous one. The product is formed after a series of β -hydride elimination, reinsertion and a 1,3 alkoxy shift (known as the Ferrier allylic rearrangement, Figure 13).

Figure 13: Ring opening with Ferrier-type rearrangement

Sonoda *et al.*^{27b, 29} performed ring opening reactions of trisubstituted cyclopropanes. They obtained an exocyclic olefin product (1-37) and proposed a 1,2-hydride shift mechanism (Figure 14). The same transformation can also be achieved by using an excess of anhydrous ZnI_2 .³⁰

Figure 14: Ring opening by Sonoda using Zeise's dimer

Sonoda *et al.* investigated the ring opening of these cyclopropanes using a rhodium catalyst.³¹ In this case, mixtures of isomeric olefins (1-40 – 1-44) were obtained due to the similar kinetic stabilities of the possible π -complex intermediates and isomerisation of the olefins (Figure 15).

Figure 15: Rhodium catalysed ring opening

The transition metal mediated ring opening of piperidine cyclopropanes was investigated previously on a model substrate (**1-45**) in our group.³² Sivarajan (a previous PhD student) screened platinum, palladium and gold complexes and found platinum and gold to be suitable for this transformation, obtaining an endocyclic olefin ring opening product (**1-46**) (Figure 16).

Figure 16: Conditions giving the best selectivity for the ring opening reactions

Based on literature examples and Sivarajan's results, a mechanism was proposed for the ring opening reactions.³² Two competing pathways were put forward which led to the two possible products. The first step is the oxidative addition of the platinum on the cyclopropane forming a platinacyclobutane intermediate (**1-49**) which is a known reaction from the work of Tipper.²⁴ This is followed by the ring opening of the platinacyclobutane promoted by the lone pair of the nitrogen yielding an iminium ion. A π -complex (**1-51**) is formed via β -hydride elimination. In this π -complex the platinum can either be reinserted than eliminated to form an endocyclic olefin product (**1-55**) or it can migrate and form the exocyclic olefin product (**1-53**) through hydride transfer (Figure 17).

Figure 17: The proposed mechanism of ring openings³²

The catalytic cycle in Figure 17 explains the two competing mechanisms, but it is not consistent with Sivarajan's results. A mixture of two products was only observed when the reaction was performed using Zeise's dimer. In case of the triflate complex, complete endo-selectivity was obtained.

The choice of counteranion ligands was based on mechanistic considerations, enabling us to investigate both positively and negatively charged platinum species in this transformation. In the case of Zeise's dimer the chloride ligand does not dissociate from the metal, providing a negatively charged platinum catalyst throughout the reaction. Changing the counteranion to triflate, we observe the formation of a positively charged catalyst due to the dissociation of the triflate, and the propanenitrile acting as a ligand. In the latter case, the migration of the platinum is not favoured, as migration towards the positive iminium ion is heavily disfavoured, ultimately leading to complete endo-selectivity (Figure 18).

Figure 18: Catalytic cycle with positively charged catalyst

1.4 Ring Opening reactions of Cyclopropanes: Results and Discussion

Our cyclopropane library was synthesised using literature examples combined with previously utilized methods of our group. The cyclopropanes (**1-56**) were obtained from the corresponding ene-sulfonamides (**1-57**) using Furukawa's modification of the Simmons-Smith cyclopropanation. The ene-sulfonamides were derived from the corresponding *N*-tosylated homoallylamines (**1-58**) through a tandem hydroformylation-intramolecular condensation (Figure 19). For the synthesis of the homoallylamines, existing literature procedures were used, since some of these (or their analogues) are known compounds. In this study only the relative stereochemistry was investigated, and because of this, all our synthetic routes involved racemic compounds.

Figure 19: Retrosynthetic analysis of cyclopropanes

A convenient synthesis of homoallylamines (**1-58**) is the *aza*-Sakurai-Hoshomi 3-component reaction.³³ This is a one-pot procedure where an aldehyde reacts with an amine and allyltrimethylsilane in the presence of a Lewis acid (Figure 20).

Figure 20: Synthesis of homoallylamine **1-62**

Aldehyde **1-60** was originally obtained from propane 1,3-diol after selective TBS-protection and IBX oxidation of alcohol **1-59**.³⁴ The yield for the oxidation was capricious (15-38%), and the resulting aldehyde was contaminated with a significant amount of TBS-related byproducts. This was due to acidic impurities in IBX³⁵, which cleaved the TBS group resulting in product loss. Changing the oxidation procedure to the Swern oxidation of **1-59**,³⁶ aldehyde **1-60** was obtained in consistently quantitative yield. However, the aldehyde was contaminated with traces of dimethyl sulfide, which had to be removed in later stages of the synthesis to avoid catalyst deactivation during hydroformylation.

Aldehyde **1-60** was subjected to the *aza*-Sakurai-Hoshomi three-component reaction with toluenesulfonamide to form the corresponding imine, then allylation took place with allyltrimethylsilane in the presence of boron trifluoride diethyl etherate³⁷ to form homoallylamine **1-61**. The TBS group was cleaved upon the addition of boron trifluoride, despite being reported to be stable under these conditions.³³

Removal of dimethyl sulphide was carried out by oxidising it with either dilute aqueous H₂O₂ or bleach. Alternatively, repeated azeotropic distillation with methanol can be used, as well as

exposing the mixture to high vacuum in the presence of blue Kieselgel. Silylation of **1-61** with TBSCl gave protected homoallylamine **1-62**.³⁴

Figure 21: Synthesis of homoallylamine **1-64**

The aza-Sakurai-Hoshomi 3-component reaction failed when 4-methoxy benzaldehyde was used, as only traces of the allylated product **1-64** were obtained. However, imine **1-63** was isolated in high yield. This imine is highly resonance stabilised, causing lower reactivity in the Sakurai-Hoshomi reaction. Allylation of imine **1-63** was optimised by screening different allylation methods. Sakurai allylation with allyltrimethylsilane and boron trifluoride resulted in *O*-demethylation. Allylmagnesium bromide provided only low conversion, even at 60 °C. The consumption of the starting material was only observed when allyl zinc bromide³⁸ was used and homoallylamine **1-64** was obtained in high yield. For subsequent batches, imine **1-63** was synthesised using 4-methoxybenzaldehyde and tosyl isocyanate³⁸ (Figure 21).

Figure 22: Retrosynthetic analysis of homoallylamine **1-65**

The aforementioned strategy did not yield imine **1-66** as methyl glyoxylate **1-67**³⁹ did not react under our conditions as anticipated. (Figure 22) Alternatively the ethyl analogue of homoallylamine **1-65** was synthesised starting from diethyl allylmalonate. Selective hydrolysis⁴⁰ was performed to yield monoacid **1-68** which was subjected to a modified Curtius

reaction⁴¹ to yield unprotected homoallylamine **1-72**. Tosylation of **1-72** yielded the desired product **1-73** (Figure 23).

Figure 23: Synthesis of homoallylamine **1-73**

Hydrolysis of isocyanate **1-71** with water yielded urethane dimer **1-74**. Amine **1-72** is a better nucleophile than water and it attacked isocyanate **1-71** upon formation. To eliminate this competing reaction, *p*-toluenesulfonic acid monohydrate in DCM was used instead of water. Amine **1-72** is trapped as its *p*-TSA salt, allowing the hydrolysis of isocyanate **1-71** by water (Figure 24).

Figure 24: Hydrolysis of isocyanate **1-71** without acid

With the homoallylamines in hand, hydroformylation was attempted to obtain cyclic ene-sulfonamides. This reaction was applied previously by our group for the synthesis of natural products.^{42, 43} For the optimization of the hydroformylation conditions³², **1-62** was used as the test substrate (Table 1, Figure 25).

Table 1: Optimization of hydroformylation conditions (Figure 24)

ligand	mol% of cat.	solvent	T (°C)	t (h)	product / yield
P(OPh) ₃	20	THF	65	18	isomeric mixture / NA
BIPHEPHOS	0.2	THF	65	18	1-75 : 1-62 = 1:2 / not isolated
BIPHEPHOS	0.2	THF	85	48	1-75 : 1-62 = 2:1 / not isolated
BIPHEPHOS	0.2	THF	85	30	1-75 / not isolated
BIPHEPHOS	0.2	PhMe	85	30	1-75 / not isolated
BIPHEPHOS	2.0	PhMe	85	23	1-76 / 88%

* Each reaction was carried out in a Fischer-Porter tube, using a 1:1 mixture of CO and H₂ (60 psi total pressure; catalyst precursor was Rh₂(OAc)₄ in each case.

Figure 25: Hydroformylation of homoallylamine **1-62**

When using triphenyl phosphite, a mixture of isomers was obtained as triphenyl phosphite has modest selectivity for linear aldehydes during hydroformylation. Changing the ligand to BIPHEPHOS,³³ the formation of the hydroxypiperidine intermediate **1-75** was observed in all of the cases when a low catalyst loading was used (0.2 mol%). The conversion was dependent on the temperature and the reaction time as well (Table 1; Figure 25).

Intermediate **1-75** was always obtained as a single diastereomer. The stereochemistry of this intermediate was proposed to be *cis* based on our previous experience with 2,6-disubstituted *N*-tosylpiperidines. The tosyl group of these compounds is pseudo-equatorial due to the flattened sp² nitrogen, and α -equatorial substituents would clash sterically with the tosyl group. It is assumed that an intramolecular H-bond exists between the hydroxyl group and the silyl ether. Increasing the amount of the catalyst and ligand to 2 mol% results in dehydration to give enesulfonamide **1-76**. It has to be noted that the Rh-catalyst is involved in the dehydration step.⁴⁴

Figure 26: Hydroformylation of homoallylamines

Lower catalyst loadings (0.2 mol% catalyst, PhMe, 85 °C, 23 h) were used for the hydroformylation of **1-64** and **1-73**, and ene-sulfonamides **1-77** and **1-78** were obtained in excellent yields (92% and 89% respectively, after column chromatography). The hydroformylation of homoallylamines **1-64** and **1-73** with 0.2 mol% and 1 mol% catalysts did not yield the hydroxypiperidine intermediates, just the cyclic ene-sulfonamide products (Figure 26).

In order to diversify our set of compounds, a 5-membered ene-sulfonamide **1-85** was added to this study. For this compound we did not use hydroformylation, but we intended to obtain our homopropargylamine through the ring opening⁴⁵ reaction of the corresponding aziridine⁴⁶ **1-82** with lithium TMS-acetylide. A complex mixture of products was obtained, where neither the ¹H NMR spectrum of the crude material nor TLC indicated product formation (Figure 27).

Figure 27: Attempted homopropargylamine synthesis through aziridine

In order to obtain dihydroxypyrrole **1-85** a silver-mediated cycloisomerisation⁴⁷ was performed on homopropargylamine **1-84**, which was synthesised in a similar way to homoallylamine **1-64** using propargylzinc bromide⁴⁸ (Figure 28).

Figure 28: Synthesis of the 5-membered ring

The cyclopropanation of ene-sulfonamides was previously investigated by our group³² and using these results, the cyclopropanation of compounds **1-76**, **1-77**, **1-78** and **1-85** to **1-86**, **1-87**, **1-88** and **1-89** respectively was achieved by the Furukawa-modified Simmons-Smith reaction using diethyl zinc and diiodomethane¹⁶ in 70-85% yield, depending on the ring size and the R substituent (Figure 29).

Figure 29: Synthesis of cyclopropanes: **1-86** ($n=1$, $R=CH_2CH_2OTBS$; 76%); **1-87** ($n=1$, $R=4-MeOC_6H_4$; 87%); **1-88** ($n=1$, $R=COOEt$; 79%); **1-89** ($n=0$, $R=4-OMeC_6H_4$; 67%)

The cyclopropanes can be identified easily by ¹H NMR spectroscopy. The protons of the peripheral methylene group of the cyclopropane ring have characteristically low chemical shifts (between -0.2 and 0.6 ppm). This can be explained by the unusual character of the C-H bonds in cyclopropanes (see Introduction). Cyclopropanated compounds **1-86**, **1-87** and **1-89** were formed as single diastereomers, however cyclopropane **1-88** ($R = CO_2Et$) was formed as a near 1:1 diastereomeric mixture according to ¹H and ¹³C NMR spectroscopy.

The stereochemistry of this reaction was presumed to be *trans* by Harrity¹⁶, but no proof has been shown yet. To our delight, cyclopropanes **1-87** and **1-89** were crystalline compounds and

were subjected to X-ray crystallography. The result confirmed the *trans* stereochemistry and this will be the first reported evidence of the stereochemistry of this reaction (Figure 30).

Figure 30: The X-ray structure of **1-87**

In the case of cyclopropane **1-88** the lack of diastereoselectivity was attributed to the possible coordination effect of the ester group. To test our theory, ene-sulfonamide **1-78** was reduced to the corresponding alcohol **1-90** which was subjected to cyclopropanation (Figure 31).

Figure 31: Cyclopropanation of CH_2OH and CO_2Et containing compounds

Cyclopropane **1-91** was formed as a single diastereomer and the stereochemistry was determined to be *trans* based on a NOESY experiment. The OH group is normally a *cis* directing group in Simmons-Smith cyclopropanations due to the strong coordination ability to zinc. In this case an excess of the zinc reagent was used and according to our hypothesis one equivalent of Et_2Zn reacted with the OH group forming an inactive ROZnEt species and a second equivalent of Et_2Zn reacted with CH_2I_2 to form the active carbenoid for the

cyclopropanation. By converting the OH group to the ROZnEt functionality, any coordinative directing group was eliminated, which yielded the *trans* cyclopropane exclusively.

Figure 32: *Trans* cyclopropane **1-91** based on NOESY spectra

According to the NOESY experiment, cyclopropane protons H_x and H_y do not show cross peaks with protons H_z , but H_x has a cross peak with H_c . H_z gave cross peak with H_b , and this data is in accordance with the proposed *trans* stereochemistry above (Figure 32).

Figure 33: Post-cyclopropanation modifications

In order to further diversify our cyclopropane library **1-86** was deprotected to yield the free alcohol **1-92**, which was converted to the allyl ether **1-93** (Figure 33). These nucleophilic side chains were investigated later in the ring opening reactions.

According to the preliminary studies discussed³², two ring opening conditions were tested on each substrate. The formation of the endocyclic ring opening product was anticipated when using $(EtCN)_4Pt(OTf)_2$ in toluene under reflux, and for the exocyclic olefin with $[Pt(C_2H_4)Cl_2]_2$ (Zeise's dimer) under the same conditions (Table 2).

endo: **1-94** (R = CH₂CH₂OH); **1-95** (R = 4-MeOC₆H₄); **1-96** (R = COOEt); exo: **1-97** (R = 4-MeOC₆H₄)

Figure 34: Transition metal mediated ring opening of cyclopropanes

Table 2: Ring opening reactions of cyclopropanes under selected conditions

R (ring size) (entry)	catalyst ^a	SM(%) ^b	endo(%) ^b	exo(%) ^b	byp(%) ^{b,c}	remark
CH ₂ CH ₂ OTBS (1-86)	(EtCN) ₄ Pt(OTf) ₂	-	-	-	100	decomposition
CH ₂ CH ₂ OTBS (1-86)	[Pt(C ₂ H ₄)Cl ₂] ₂	-	-	-	100	decomposition
CH ₂ CH ₂ OH (1-92)	(EtCN) ₄ Pt(OTf) ₂	-	100	-	-	
CH ₂ CH ₂ OH (1-92)	[Pt(C ₂ H ₄)Cl ₂] ₂	-	100	-	-	
CH ₂ CH ₂ Oallyl (1-93)	(EtCN) ₄ Pt(OTf) ₂	-	-	-	100	decomposition
CH ₂ CH ₂ Oallyl (1-93)	[Pt(C ₂ H ₄)Cl ₂] ₂	-	-	-	100	decomposition
4-MeOC ₆ H ₄ (6) (1-87)	(EtCN) ₄ Pt(OTf) ₂	-	67	-	23	
4-MeOC ₆ H ₄ (6) (1-87)	[Pt(C ₂ H ₄)Cl ₂] ₂	-	55	45	-	
4-MeOC ₆ H ₄ (5) (1-89)	(EtCN) ₄ Pt(OTf) ₂	-	-	-	100	decomposition
4-MeOC ₆ H ₄ (5) (1-89)	[Pt(C ₂ H ₄)Cl ₂] ₂	100	-	-	-	SM recovered
COOEt (1-88)	(EtCN) ₄ Pt(OTf) ₂	-	100	-	-	
COOEt (1-88)	[Pt(C ₂ H ₄)Cl ₂] ₂	-	100	-	-	

^a: 0.1 eq catalyst, toluene, 110°C, 14 h, ^b: ratio of the compounds in the crude ¹H NMR, ^c: by-product

Our results did not completely correlate with the ones reported by Kasinathan³², where Zeise's dimer yields predominantly the *exo* product (see Figure 16). Only the *p*-methoxyphenyl substrate mirrored the results obtained by him. All other substrates showed either decomposition or complete endo-selectivity, for which we are unable to provide an explanation at this point.

Besides investigating the selectivity, the functional group tolerance of this reaction was also of our interest. The results showed that TBS ether **1-86** and allyl ether **1-93** were unstable under

both conditions, while the free alcohol **1-92**, ester **1-88** and the aromatic group in **1-87** were proven to be stable. The five-membered ring **1-89** was suspected to react readily because of the higher ring strain, but surprisingly it decomposed when (EtCN)₄Pt(OTf)₂ was used as a catalyst, and it did not undergo any reaction with Zeise's dimer (Table 2).

As it did not react as it was anticipated, five-membered compound **1-89** was further investigated. It was reacted with 1 equivalent of Zeise's dimer in benzene-*d*₆ at elevated temperature and the ¹H NMR spectrum of this experiment showed that some kind of reaction had taken place. According to our hypothesis, the catalyst reacts with the cyclopropane in the catalytic reaction resulting in decomposition, while the unreacted cyclopropane is recovered.

It was observed that intramolecular nucleophiles did not trap the iminium ion intermediate (Table 2). A logical step was to investigate if nucleophilic additives were able to trap the iminium anion. Additionally, their effect on the *endo/exo* selectivity was investigated as well.

Since the most versatile reactivity and the greatest stability was obtained in the case of the piperidine containing the 4-methoxyphenyl side chain **1-87**, experiments were carried out on this substrate only from this point onwards.

In case of the (EtCN)₄Pt(OTf)₂ catalysed reactions (Table 3) 100% selectivity was obtained for the endocyclic product, but an unidentified by-product was formed as well, which resulted in the isolated yield of the endocyclic olefin never exceeding 50%. As preliminary studies³² showed that these reactions proceed at lower temperatures as well, an optimum temperature was found to be 80°C where a product:by-product ratio of 79:21 was observed as opposed to the original 67:33. Lowering the temperature even more gave interesting results: at 60°C the formation of the exocyclic product was obtained as well, which is unexpected and can not be explained at this point. The *endo:exo* ratio was found to be 69:17, but the reaction was not

complete, 14% starting material was still present. Unfortunately, the *endo* product was difficult to separate from the by-product, even at the optimized conditions, it was isolated in 55% yield.

In the case of the Zeise's dimer catalysed reactions (Table 3), the *exo*-selectivity was attempted to be improved through a temperature screening. Higher temperatures yielded better selectivity, but the *exo:endo* ratio never exceeded 2:1, not even at 150°C.

Table 3: Optimization of ring opening reactions (% determined by crude ¹H NMR)

catalyst	T / °C	solvent	additive	eq	SM (%)	<i>endo</i> (%)	<i>exo</i> (%)	by-product (%)
(EtCN) ₄ Pt(OTf) ₂	110	MeOH	-	-	76	24	-	-
(EtCN) ₄ Pt(OTf) ₂	110	PhMe	MeOH	130	83	17	-	-
(EtCN) ₄ Pt(OTf) ₂	60	PhMe	-	-	14	69	17	-
(EtCN) ₄ Pt(OTf) ₂	80	PhMe	-	-	-	79	-	21
(EtCN) ₄ Pt(OTf) ₂	100	PhMe	-	-	-	64	-	36
(EtCN) ₄ Pt(OTf) ₂	110	PhMe	-	-	-	67	-	33
(EtCN) ₄ Pt(OTf) ₂	80	PhMe	BnOH	1	-	62	-	38
(EtCN) ₄ Pt(OTf) ₂	80	PhMe	TFE	1	-	69	trace	31
(EtCN) ₄ Pt(OTf) ₂	80	PhMe	pMeOC ₂ H ₄ OH	1	-	67	-	33
(EtCN) ₄ Pt(OTf) ₂	110	PhMe	allylTMS	1	-	77	-	23
(EtCN) ₄ Pt(OTf) ₂	80	PhMe	AcOH	1	-	74	-	26
[Pt(C ₂ H ₄)Cl ₂] ₂	110	PhMe	-	-	-	55	45	-
[Pt(C ₂ H ₄)Cl ₂] ₂	60	PhMe	-	-	-	84	16	-
[Pt(C ₂ H ₄)Cl ₂] ₂	80	PhMe	-	-	-	76	24	-
[Pt(C ₂ H ₄)Cl ₂] ₂	100	PhMe	-	-	-	59	41	-
[Pt(C ₂ H ₄)Cl ₂] ₂	80	PhMe	BnOH	1	-	70	trace	30
[Pt(C ₂ H ₄)Cl ₂] ₂	80	PhMe	TFE	1	-	33	67	-
[Pt(C ₂ H ₄)Cl ₂] ₂	80	PhMe	pMeOC ₂ H ₄ OH	1	-	38	62	-

[Pt(C ₂ H ₄)Cl ₂] ₂	80	PhMe	AcOH	1	-	27	73	-
[Pt(C ₂ H ₄)Cl ₂] ₂	130	PhMe	TFE	1	-	50	50	-
[Pt(C ₂ H ₄)Cl ₂] ₂	130	PhMe	TFE	10	-	38	62	-
[Pt(C ₂ H ₄)Cl ₂] ₂	150	PhMe	TFE	50	-	39	61	-

In the case of the (EtCN)₄Pt(OTf)₂ catalysed reactions with nucleophilic additives, no addition products were isolated. The *endo*:by-product was ratio was affected, but not in a significant way.

In the case of the Zeise's dimer catalysed reactions (Table 3) no addition products were isolated, but the additives had a significant effect on the *exo*:*endo* ratio. Both trifluoroethanol, 4-methoxyphenol and acetic acid improved the *exo* selectivity to 73:27. Combining these additives with elevated temperatures did not result in any further improvement. Interestingly, when benzyl alcohol was added, complete *endo* selectivity was obtained, but an unidentified by-product was formed as well, in 70:30 *endo*:by-product ratio.

The trapping of the iminium ion with nucleophilic additives was not observed, which means that there was no free iminium ion present during the reactions for a sufficiently long time to be trapped.

Next, the reaction of the endocyclic ring opening product **1-95** with nucleophiles was investigated. The diastereoselective allylation of cyclic ene-sulfonamides was reported by Harrity⁴⁹, but this method did not work on our substrate (Figure 35).

Figure 35 Allylation method by Harrity (left), allylation by us (right)

It was suspected that the allylation is not taking place due to the increased steric hindrance by the methyl group, the reaction was repeated with a stronger nucleophile, *p*-thiocresol. While the addition was successful, it resulted in a 1:1 inseparable mixture of diastereomers (**1-103**) (Figure 36).

Figure 36: Addition of thiocresol

It was anticipated that the separation of diastereomers could be performed on the corresponding sulfone, but oxidation of the mixture was not successful. A method described by Ley was also investigated,⁵⁰ where he used *p*-toluenesulfinic acid as the nucleophile. The formation of the desired product was not observed, likely due to the lower nucleophilicity of the ArSO_2^- anion. It was concluded that we were unable to obtain any addition products on these substrates.

Another interesting concept was the ring opening of cyclopropanes where the β -hydrogen substituent is absent. As the β -hydride elimination is an important step in the catalytic cycle, it was of interest to investigate the consequences of β -blocking. The synthesis of such a compound seemed convenient, since it can be obtained *via* the cyclopropanation of the endocyclic ring opening product **1-92**. The cyclopropanation procedure which was used earlier¹⁶ (Et_2Zn , CH_2I_2) was not suitable in this case: a significant amount of a by-product was formed, which will be discussed later.

As an alternative, chloromethylzinciodide, a more powerful cyclopropanating agent was used.⁵¹ This allowed the target cyclopropane to be formed in a reasonable yield as a single diastereomer (Figure 37) and the sole product of the reaction. Another method was tested using Me_3Al and

CH₂I, but it did yield any product.⁵² The *trans* stereochemistry of **1-104** was assigned based on the analogy to our previous results (eg **1-86**, **1-87**, **1-89**).

Figure 37: Cyclopropanation with improved conditions

Ring opening of this cyclopropane gave us interesting results (Figure 38). When the positively charged platinum catalyst - $(\text{EtCN})_4\text{Pt}(\text{OTf})_2$ – was used, the piperidine ring was opened, probably due to reaction with adventitious moisture and aldehyde **1-105** was isolated.

Figure 38: Ring opening resulting in an unexpected product

The formation of aldehyde **1-105** can be explained by a proposed mechanism below (Figure 39).

Figure 39: Proposed mechanism for the formation of aldehyde **1-105**

To our delight, the ring opening reaction with Zeise's dimer resulted in an even more interesting discovery: the ring opening was performed, and an exocyclic olefin was obtained as a single *cis* diastereomer (Figure 40).

Figure 40: Ring opening with Zeise's dimer

The *cis* stereochemistry was based on a NOESY experiment which showed a cross peak between the α -methyl group and α -aryl proton, no cross peak was observed between the two protons α to the nitrogen. Furthermore, neither of the α -protons showed a cross peak with either the α -methyl and α -aryl groups, indicating that both the methyl and aryl group are in the axial position. Compound **1-106** was found to be crystalline and was subjected to X-ray crystallography to confirm the *cis* stereochemistry (Figure 41).

Figure 41: Xray structure of **1-106**

There are several possible explanations for the mechanism of this reaction (Figure 42).

Figure 42 Possible catalytic pathways for cyclopropane ring opening where no β -hydrogen is present

Regardless of which mechanism is correct, it is important to note that the result is in accordance with the previously proposed catalytic cycle³²: the original substituent in position 3 will migrate one way or another onto the iminium ion in position 2, both resulting in *cis* stereochemistry. The two possible pathways include either a Wagner-Meerwin type 1,2-alkyl shift or a β -carbon elimination which is analogous to the β -hydride elimination in the original mechanism.

In order to confirm which carbon is the source of the α -methyl group in the product, an isotope labelling experiment was performed. Ene-sulfonamide **1-77** was cyclopropanated using CD_2I_2 to obtain cyclopropane **1-114** with a double deuterium label. This was subjected to ring opening isomerisation yielding the endocyclic product which was cyclopropanated using the procedure described earlier (Et_2Zn , CH_2ICl). Cyclopropane **1-116** bearing a CD_2H group in the *beta* position was subjected to our reaction conditions with Zeise's dimer yielding a product where

the integral of the *alpha* methyl group was decreased from 3 to 1 in the ^1H NMR indicating a CD_2H group having migrated to the α -position (Figure 43). This confirms the methyl group migration.

Figure 43: Isotope labelling experiment

With these results and methods, it is impossible to distinguish between the proposed mechanisms, but the hypothesis of the Wagner-Meerwein shift is more plausible due to the much lower activation energy of the 1,2-alkyl shift compared to the β -C elimination.

Figure 44: Ring opening pathway supporting the alkyl-migration theory

The reaction proceeded to 50% conversion with 10 mol% of Zeise's dimer upon heating at reflux overnight. Further experiments were performed in order to drive the reaction to completion. It was observed that longer reaction times resulted in lower yields, which indicated

that the product olefin was not stable under these conditions. Also, the reaction was performed at room temperature and TLC analysis indicated the product formation in the first 16 hours, but after additional 24 hours, the product spot has disappeared. Even after a series of optimisations, the reaction could not be driven to completion, and the conversions measured by ^1H NMR were not always reproducible.

Experiments were conducted investigating the effects of temperature, solvent, catalyst loading, additives and the catalyst. Certain changes gave better conversions, but combining these factors did not result in further improvements. Significant success was observed when the solvent was changed to DCE or the catalyst loading was increased. The temperature window for this reaction was discovered to be quite narrow: temperatures both lower and higher than 85-110°C gave low conversions. The reaction did not proceed in acetonitrile, and dioxane only offered low conversion. No product was obtained when using Vaska's complex. $(\text{EtCN})_2\text{PtCl}_2$ also gave low conversion. Additives like PPh_3 , PCy_3 , Ph_2CHCN or COD inhibited the reaction and the starting material was recovered. The highest conversion achieved was 42% based on the ^1H NMR spectrum of the crude material using DCE with 0.2 eq Zeise's dimer at 85 °C for 16 hours. To the best of our knowledge, this is the first reported example of a platinum driven 1,2-alkyl shift reaction.

Regardless of the obtained mechanistically interesting results, it was concluded that none of these approaches can be used in alkaloid total synthesis. The following chapters will discuss a long journey which was inspired by an unexpected side reaction and ultimately led to the total synthesis of several piperidine alkaloids

1.5: Rediscovery of the Prins Reaction

Investigation of a serendipitous discovery led us to an interesting reaction. A cyclopropanation was performed during the previous study using Furukawa's conditions⁵³ as reported by Harrierty¹⁶, where the formation of another product was observed in about 1:1 ratio to the target cyclopropane. The structure was identified using NMR, MS and X-ray crystallography which showed that a bicyclic piperidino-1,3-dioxane (**1-121**) was formed. This seemed rather odd, since none of the reagents contained any oxygen atoms, but a dioxane ring was formed (Figure 45).

Figure 45: Serendipitous rediscovery of the Prins reaction

Since the amount of the dioxane product was significant and it was formed as a single diastereomer it was decided to investigate this reaction. This transformation was found to be an example of the Prins reaction.

Figure 46: X-ray structure of the dioxane product **1-121**

The structure of the Prins product was confirmed using a combination of NMR techniques and ultimately proven by X-ray crystallography (Figure 46). This compound contains a quaternary

carbon stereogenic centre, which was formed with complete stereoselectivity. The formation of these type of chiral centres are very difficult, making this transformation valuable. Moreover, for the first time a compound was obtained which contains an equatorial substituent α to the sulphonamide functionality. This is extremely unusual, as the tosyl group occupies a pseudo-equatorial position due to the flattened sp^2 nitrogen. An α -equatorial substituent in this case is causing a steric clash. A true evidence for π -stacking can also be observed in the X-ray structure of this compound.⁵⁴

Figure 47: NMR spectrum of the Prins product

The NMR spectrum shows a singlet at 1.1 ppm with an integral of 3, indicating an isolated methyl group. According to this, a substituent was incorporated into position 3. A singlet at 5.4 ppm which corresponds to the proton α to the nitrogen indicates that this proton has to be connected to another heteroatom, as no coupling can be observed. The roofing doublet and the doublet of doublets at 4.88 and 5.20 ppm respectively indicates an isolated CH_2 group between two heteroatoms and some long-range coupling. Another pair of roofing doublet and doublet

of doublets can be found at 3.55 and 3.68 ppm respectively. This corresponds to another isolated CH₂ group with some long-range coupling, but the lower chemical shift indicates the presence of only one heteroatom. These two isolated CH₂ couple with each other (as it can be seen by the roofing effect of the dd signals) and they are separated by heteroatoms.

1.6 Prins Reaction: Literature Review

The mutual condensation of alkenes and formaldehyde⁵⁵ resulting in the formation of 1,3-dioxanes was reported by Hendrik Jacobus Prins in 1919. He reacted simple olefins and terpenes with formaldehyde in the presence of aqueous sulphuric or acetic acid and obtained the products in 70-90% yield, although he reported the formation of a mixture of compounds. In the case of strongly acidic media the main product was 1,3-dioxane **1-123**. The reaction was not of great significance at that time, but as the oil cracking industry developed and various olefins became easily accessible, the method has gained increasing attention.

Figure 48: The Prins reaction

Throughout the past century many applications and modifications of the Prins reaction⁵⁶ have been developed and today the Prins reaction is mostly used for the synthesis of tetrahydropyrans. The original version of the reaction yielding 1,3-dioxanes was of our interest with focus on the Brønsted acid free conditions.

Figure 49: The acid catalysed Prins reaction

The original reaction was the acid catalysed mutual condensation of olefins and formaldehyde, where mechanistic studies proposed a protonated formaldehyde dimer **1-125** as the reaction partner for the olefin (Figure 49).⁵⁷ The mechanism involves a series of equilibrium reactions where the product exists as a mixture of cyclic **1-127** and linear forms **1-126**. Because of this, diastereoselectivity can not be achieved (Figure 50).

Figure 50 The acid-mediated equilibrium of diastereomeric products

This classical approach requires rather harsh conditions (strong mineral acids, elevated temperatures) and this strongly limits the scope of the reaction for delicate substrates. Some approaches targeted milder Brønsted acidic conditions using Wells-Dawson type heteropolyacids ($\text{H}_3\text{PW}_{12}\text{O}_{40} \cdot 25\text{H}_2\text{O}$, etc) which were proven to be effective in the synthesis of 1,3-dioxanes.⁵⁸

One of the simplest approaches was reported by Sreedhar *et al.*⁵⁹ $\text{Bi}(\text{OTf})_3$ was utilised as an efficient Lewis acid catalyst for the Prins reaction of styrenes in refluxing acetonitrile.

A Prins reaction under non-conventional conditions was reported by Chandrasekhar and Reddy.⁶⁰ A $\text{TaCl}_5/\text{SiO}_2$ catalytic system was utilised for the transformation of styrenes and related compounds. It was also discovered that solventless microwave irradiation (3-5 min) was much more effective than conventional heating (12-14 h, refluxing dioxane).

Yadav *et al.*⁶¹ utilized InBr_3 as a catalyst in 1-butyl-3-methylimidazolium hexafluorophosphate ($[\text{bmim}]\text{PF}_6$) which was efficient for styrenes and stilbenes as well. In case of *trans* stilbenes, the resulting dioxane was formed diastereoselectively.

Another diastereoselective method was developed by Bach and Lobel.⁶² They utilized sterically congested Lewis acids such as 2,6-di-tert-butylphenoxy(difluoro)borane which enabled them to obtain moderate diastereoselectivity in case of stilbenes and related compounds.

A metal-free approach was discovered by Yadav *et al.*⁶³ They have reported conditions utilizing molecular iodine as the Lewis acid in the transformation of styrenes and related compounds. So far this was the mildest method published: a stoichiometric amount of all reagents; dichloromethane; room temperature; 40-90 minutes. Although in this case the *in situ* formation of HI could lead to Brønsted acid catalysis.

Figure 51: The most common literature example: transformation of styrene

As it was shown, the literature of Lewis-acid catalysed Prins reactions yielding 1,3-dioxanes does not contain too many approaches for this transformation. And even the existing methods were only described using simple substrates as styrenes, stilbenes and a few aliphatic terminal olefins. Our approach is the first reported one for the Prins reaction of *N*-tosylated ene-sulfonamides. Through this transformation, valuable *N,O*-acetals are readily available diastereoselectively.

1.7 Prins Reaction: Results and Discussion

Since the cyclopropanation was performed under inert conditions, it seemed to be strange that a dioxane product was formed, as none of our reagents contained any oxygen. The only viable explanation was a leakage in the reaction flask and molecular oxygen interfering with the Furukawa cyclopropanation. In order to establish a hypothesis, the mechanism of this cyclopropanation had to be investigated.

According to the literature, a possible active reagent of the Furukawa cyclopropanation reaction is $\text{Zn}(\text{CH}_2\text{I})_2 \cdot \text{ZnI}_2$.⁶⁴ This reagent has a long half-life, and assuming that the initial reaction of diethyl zinc and diiodomethane results in the formation of $\text{Zn}(\text{CH}_2\text{I})_2 \cdot \text{ZnI}_2$, a mechanism can be proposed for the oxidation of carbenoid **1-132**, which is the synthetic equivalent of zinc iodide and formaldehyde (Figure 52).

Figure 52 Theoretical oxidation pathway of zinc carbenoid

According to our hypothesis the dioxane ring was constructed from 2 moles of *in situ* generated formaldehyde in the presence of a Lewis acid. Formaldehyde is not stable in solution, in fact it tends to polymerize instantly, even at lower temperatures. In this case the formaldehyde concentration is low due to the *in situ* generation and it reacts with the ene-sulfonamide faster than it polymerises (Figure 53).

Figure 53: Possible coordination of the carbenoid and *in situ* oxidation to formaldehyde

The formation of the dioxane product can be explained by a stepwise mechanism if monomeric formaldehyde is present. The nucleophilic attack of the enamine occurs on the Lewis acid activated formaldehyde. The resulting alcoholate **1-132** acts as the next nucleophile and attacks another activated formaldehyde. Ring closure is achieved by the addition of the new alcoholate **1-133** to the iminium ion (Figure 54).

Figure 54: Proposed mechanism of the formation of 1,3-dioxane product

The Prins product was formed as a single diastereoisomer. The formation of the first stereocenter is analogous to the cyclopropanation reaction, while the formation of the second one proceeds under stereoelectronic control. The ring must flip in order to achieve the intramolecular nucleophilic attack resulting in a chair transition state (Figure 55).

Figure 55: Origin of stereoselectivity in the Prins reaction

It was anticipated that the same transformation can be achieved by simply mixing the enesulfonamide with ZnX_2 and formaldehyde. Common formaldehyde sources are paraformaldehyde (the linear polymer) and 1,3,5-trioxane (the cyclic trimer) and they can be cracked into monomeric formaldehyde by heating or upon treatment with a Lewis acid. Anhydrous zinc halides are highly hygroscopic and commercially available. Once their container is being opened they cease to be anhydrous and they have to be dried prior to use or generated *in situ*.

In order to validate our hypothesis, a Prins reaction was performed on the same endocyclic olefin **1-95** which was the starting material for the cyclopropanation reaction where the Pins product was first obtained.

Under our initial conditions (ZnCl_2 , paraformaldehyde, DCM, 25°C , 15 h) the endocyclic olefin was converted into the previously obtained Prins product in 25% yield and the product was obtained as the same single diastereomer as before (Figure 56).

Figure 56: Reproducing the Prins reaction using simple reagents

With this preliminary result in hand, another substrate was subjected to these conditions as well. Ene-sulfonamide **1-77** was chosen as the test substrate which does not contain the methyl group in position 3. This turned out to be a crucial feature in the reaction, since no Prins product **1-135** was obtained, only the dimer **1-136** (Figure 57, Table 4).

Figure 57: Prins reaction of the non-methyl containing ene-sulfonamide

In this small optimisation study, since the obtained product was not the desired one, isolation was not performed, just the crude ^1H NMR spectra were recorded. Also, there was no extensive effort to optimise the Prins reaction on this substrate, as we intended to use this transformation on a different class of substrates (see Chapter2).

Table 4: Summary of Prins reaction conditions

Lewis acid	"CH ₂ O"	T / °C	solvent	product	conversion from 1-77
ZnCl ₂	paraformaldehyde	0	DCM	dimer	50 % conversion
ZnCl ₂	paraformaldehyde	25	DCM	dimer	100 % conversion
ZnCl ₂	paraformaldehyde	40	DCM	dimer	100 % conversion
ZnCl ₂	paraformaldehyde	25	PhMe	dimer	80% conversion
ZnCl ₂	paraformaldehyde	25	THF	SM	no product obtained
ZnI ₂	paraformaldehyde	50	THF	Prins	8% conversion
ZnCl ₂	trioxane	40	DCM	dimer	low conversion
ZnCl ₂	trioxane	110	PhMe	dimer	high conversion, messy

In most of the cases the dimer product **1-136** was obtained. The ^1H NMR spectrum contains every peak twice, which indicates a mixture of *dl* and *meso* compounds, and the integrals of the peaks suggest dimers as well. As for the mechanism, it was postulated that the addition of the first formaldehyde happens readily, but the β -hydrogen abstraction by the halide anion present is faster than the reaction of the alcoholate with another formaldehyde due to the low concentration of monomeric formaldehyde (Figure 58).

Figure 58: Dimerisation of ene-sulfonamides

Several conditions were screened to explore the $\text{ZnCl}_2/(\text{CH}_2\text{O})_n$ system by varying the solvent and the temperature. In dichloromethane the reaction proceeded smoothly yielding the dimer product with high conversion. Lowering the temperature decreased the conversion but did not allow the Prins product to be formed. Toluene gave the same result, but the reaction proceeded with slightly lower conversion. In THF – which is a Lewis base – no product formation was observed whatsoever due to the strong coordination of THF to the ZnCl_2 . The only instance where the formation of the Prins product was observed was when ZnI_2 was used, but the conversion was very low (8%) due to the coordination effect of THF. Unfortunately, a solution of ZnI_2 in non-Lewis basic solvents such as dichloromethane or toluene could not be generated. Trioxane was tried as an alternative formaldehyde source, but it yielded either low conversions or highly multicomponent product mixtures, from which the dimer product could not be isolated.

1.8 Conclusion and Summary

A library of cyclic ene-sulfonamides was synthesised using a hydroformylation-intramolecular condensation cascade of N-tosyl homoallylamines utilized by our group for the total synthesis of piperidine alkaloids.

These ene-sulfonamides were cyclopropanated and the platinum-mediated ring opening reactions of these compounds were studied. Conditions were identified which are 100% selective for the endocyclic ring opening product which were used for further studies. Furthermore, evidence has been provided for the first time proving the *trans* selectivity of the Furukawa modified Simmons-Smith cyclopropanation reaction.

The original approach of trapping the iminium ion during ring opening reactions failed and it was performed in an additional step yielding 1:1 inseparable diastereomeric mixture.

The endocyclic ring opening product was cyclopropanated and a competitive reaction was discovered which was identified as the Prins reaction, and it gave access to the Prins product with complete diastereoselectivity.

The cyclopropanation conditions were optimised to eliminate the Prins pathway and the methyl-substituted cyclopropane was obtained and subjected to platinum-mediated ring opening reactions. Using Zeise's dimer an interesting diastereopure product was obtained and a platinum induced Wagner-Meerwein type 1,2-alkyl shift reaction was shown for the first time. The mechanism was investigated using isotope labelling experiments.

1.9 Experimental and Methods

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware. Anhydrous DCM was freshly distilled from CaH₂ under nitrogen, anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen, anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous ethanol and methanol were distilled from activated magnesium under nitrogen. All chemicals were obtained from Alfa Aesar, Strem or Sigma Aldrich and used as received. Column chromatography was carried out on silica gel, 230-400 mesh. Purity of the reported compounds was established by comparing the integrals of the peaks belonging to the compounds to the ones arising from impurities. NMR spectra were recorded on Bruker AV300, JEOL ECA400SL or JEOL ECA400 spectrometers in CDCl₃ solutions. Chemical shifts are given in ppm and coupling constants in Hz (CDCl₃ ¹H: 7.26 ppm, ¹³C: 77.23 ppm).

3-((tert-butyldimethylsilyl)oxy)propanal (1-60): To a solution of propane-1,3-diol (3.6 mL, 50 mmol) and imidazole (790 mg, 11 mmol) in anhydrous THF (22 mL) was added *tert*-butylchlorodimethylsilane (1.50 g, 10 mmol) in anhydrous THF (7.5 mL) at 0°C. Cooling was removed after 30 min, and stirring was continued for 4h. Sat. aq. NH₄Cl solution (10 mL) was added, and the mixture was extracted with twice with Et₂O. The combined organic layers were washed with water and with brine. The organic layer was dried over anhydrous MgSO₄, then filtered and concentrated. Product was obtained as a colourless liquid: 1.93 g (10.1 mmol), yield: 92%. (¹H NMR (400 MHz, CDCl₃) δ 3.80 – 3.70 (m, 4H), 2.95 (brs, 1H), 1.72 (qint, *J* = 5.7 Hz, 2H), 0.85 (s, 9H), 0.03 (s, 6H).¹ Oxalyl chloride (2.98 mL, 34.2 mmol) was dissolved in DCM (260 mL) under N₂ and cooled to -78°C. DMSO (4.14 mL, 57.8 mmol) was added dropwise over 5 min, and the mixture was stirred for 10 min. Mono-TBS protected propanediol

¹ Spectrum in accordance with: Smith, A.B., III.; Fox, R.J.; Vanecko, J.A. *Org. Lett.* **2005**, 7, 3099.

(5.0 g, 26.2 mmol) was dissolved in DCM (15 mL) and it was added to the other solution dropwise over 20 min. Immediately after that Et₃N (18.3 mL, 131.4 mmol) was added over 5 min. The mixture was stirred at -78°C for 2 h than warmed up to 0°C and it was quenched with 100 mL water. The aqueous layer was extracted three times with Et₂O. The combined organic layers were washed with water, 2M aq. HCl, sat.aq. NaHCO₃, water and brine. The combined organics were dried over anhydrous MgSO₄, then filtered and concentrated. **1-60** was obtained as a colourless liquid: 4.36 g (23.2 mmol), 88% yield. (¹H NMR (300 MHz, CDCl₃) δ 9.80 (t, *J* = 1.8 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 2.59 (td, *J* = 6.0, 2.0 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H).²

N-(1-hydroxyhex-5-en-3-yl)-4-methylbenzenesulfonamide (**1-61**): To a solution of p-toluenesulfonylamide (3.82 g, 22.3 mmol) and aldehyde **1-60** (4.2 g, 22.3 mmol) in DCM (120 mL) was added allyltrimethylsilane (3.22 mL, 22.3 mmol) at 0°C followed by BF₃•OEt₂ (3.31 mL, 26.8 mmol) and stirred 18 h, while warming up to 25°C. Sat. aq. NaHCO₃ was added than extracted three times with DCM. The combined organic layers were dried over anhydrous MgSO₄ than filtered and concentrated. **1-61** was obtained as a colourless oil: 3.48 g (12.9 mmol), 58% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.47 (ddt, *J* = 17.1, 10.2, 7.3 Hz, 1H), 5.07 (d, *J* = 8.4 Hz, 1H), 5.01 – 4.86 (m, 2H), 3.94 – 3.73 (m, 1H), 3.73 – 3.57 (m, 1H), 3.57 – 3.40 (m, 1H), 2.62 – 2.49 (m, 1H), 2.44 (s, 3H), 2.18 – 1.98 (m, 1H), 1.75 (ddd, *J* = 13.9, 9.3, 4.3 Hz, 1H), 1.57 – 1.41 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 143.7, 137.9, 133.2, 129.9 (2C), 127.3 (2C), 119.2, 59.0, 50.7, 39.7, 37.0, 21.7; FTIR (neat,

² Spectrum in accordance with Wang, J., Chen, J., Kee, C.W., Tan, C. *Angewandte Chemie International Edition* **2012**, 51, 2382.

cm⁻¹) $\nu_{\max}$ 3518, 1643, 1319, 918; MS (ESI+) m/z 270 (MH⁺, 100), 292 (MNa⁺, 75); HRMS calcd for C₁₃H₁₉NO₃Si (MNa⁺) 292.0983; found 292.0981

N-(1-((*tert*-butyldimethylsilyl)oxy)hex-5-en-3-yl)-4-methylbenzenesulfonamide (**1-62**): To a solution of **1-61** (485 mg, 1.8 mmol) and imidazole (136 mg, 1.98 mmol) in THF (15 ml) was added *tert*-butylchlorodimethylsilane (270 mg, 1.8 mmol) in THF (1.35 mL) at 0°C. Cooling was removed after 30 min, then stirred for 4h. Sat. aq. NH₄Cl solution (2 mL) was added, and the mixture was extracted twice with Et₂O and with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ then filtered and concentrated. **1-62** was obtained as a colourless oil, 579 mg (1.5 mmol), yield: 83%.

¹H NMR (396 MHz, CDCl₃) δ 7.75 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.63 (ddt, J = 17.1, 10.3, 7.2 Hz, 1H), 5.39 (d, J = 6.8 Hz, 1H), 5.05 – 4.95 (m, 2H), 3.72 – 3.60 (m, 1H), 3.55 – 3.45 (m, 1H), 3.44 – 3.31 (m, 1H), 2.42 (s, 3H), 2.35 – 2.15 (m, 2H), 1.68 – 1.44 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 143.0, 138.1, 133.8, 129.5 (2C), 127.1 (2C), 118.1, 60.1, 51.9, 39.2, 35.6, 25.8 (3C), 21.4, 18.0, -5.5, -5.4; FTIR (neat, cm⁻¹) $\nu_{\max}$ 1641, 1327, 1026, 916; MS (ESI+) m/z 384 (MH⁺, 100), 406 (MNa⁺, 22); HRMS calcd for C₁₉H₃₄NO₃SSi (MH⁺) 384.2029; found: 384.2028.

N-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (**1-63**): 4-methoxybenzaldehyde (2.04 g, 15 mmol) and *p*-toluenesulfonyl isocyanate (2.955 g, 15 mmol) were heated to 110°C in toluene (100 mL) under N₂ for 62 h, then solvent was evaporated. **1-63** was obtained as a yellow solid, 4.46 g, 90% yield, which was used in the next step without further purification. (¹H NMR (300 MHz, CDCl₃) δ 8.94 (s, 2H), 7.89 (d, J = 3.0 Hz, 2H), 7.86 (d, J = 3.0 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 3.88 (s, 3H), 2.43 (s, 3H).³

³ Spectrum in accordance with: Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.

N-(1-(4-methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (**1-64**): Zn powder (5.56 g, 85.6 mmol) was slurried in anhydrous THF (80 ml) under nitrogen. 1,2-dibromoethane (0.247 mL, 2.85 mmol) was added than the mixture was heated to ebullition than stirred for a few minutes. After this procedure was repeated 3 times, the mixture was cooled to 25°C. Trimethylchlorosilane (0.425 mL, 3.37 mmol) was added slowly, than the mixture was stirred for 15 min. Allyl bromide (2.46 mL, 28.5 mmol) was added dropwise over 20 min and the mixture was stirred for 1 h. The resulting allylzinc bromide solution was cannulated to a solution of **1-63** (5.00 g, 17.3 mmol) in THF (50 mL) at 0°C under nitrogen. The mixture was stirred for 18 h, while warming up to 25°C. The reaction was quenched with sat. aq. NH₄Cl and extracted three times with Et₂O. The combined organic layers were washed twice with sat. aq. NaHCO₃ and brine. The organic layer was dried over anhydrous MgSO₄ than filtered and concentrated. **1-64** was obtained as an off-white solid, 5.34 g (16.1 mmol), yield: 93%. (¹H NMR (396 MHz, CDCl₃) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 5.58 – 5.43 (m, 1H), 5.10 – 5.00 (m, 2H), 4.73 (d, *J* = 6.1 Hz, 1H), 4.38 – 4.27 (m, 1H), 3.76 (s, 3H), 2.52 – 2.40 (m, 2H), 2.38 (s, 3H).⁴

ethyl 2-((4-methylphenyl)sulfonamido)pent-4-enoate (**1-73**): To diethyl allylmalonate (5.00 g, 25 mmol) in anhydrous EtOH was added KOH (1.40 g, 25 mmol) in 25 ml EtOH and the mixture was stirred for 22 h, than concentrated. The residue was dissolved in a sufficient amount of water, and washed twice with Et₂O. The aqueous layer was acidified to pH 1 with 2 M aq. HCl than extracted 3 times with Et₂O. The organic extracts were dried over anhydrous MgSO₄ than filtered and concentrated. Monoacid **1-68** was obtained as a colourless liquid, 3.24 g (18.8mmol), yield: 75%. (¹H NMR (400 MHz, CDCl₃) δ 9.41 (brs, 1H), 5.87 – 5.68 (m, 1H),

⁴ Spectrum in accordance with: Wilsdorf, M.; Lechnitz, D.; Reissig, H. *Org, Lett.* **2013**, *15*, 2494.)

5.14 (d, $J = 16.9$ Hz, 1H), 5.08 (d, $J = 10.1$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.54 – 3.42 (m, 1H), 2.66 (t, $J = 7.2$ Hz, 2H), 1.27 (t, $J = 7.1$ Hz, 3H).⁵ Monoacid (580 mg, 3.38 mmol) was dissolved in anhydrous DCM (5 mL) then oxalyl chloride (0.35 mL, 4.06 mmol) in anhydrous DCM (1 mL) was added followed by 1 drop of DMF. The mixture was stirred at 25°C for 2 h, then concentrated. The residue was dissolved in DCM (5 mL) and tetra-*n*-butylammonium bromide (3.5 mg, 0.01 mmol) was added and the mixture was cooled to 0°C. Sodium azide (275 mg, 4.23 mmol) in water (1 mL) was added slowly and the mixture was stirred at this temperature for 2 h. The layers were separated, and the organic layer was washed with 2x1 mL water. Anhydrous MgSO₄ was added to the organic layer and the mixture was stirred for 20 h at 25°C and filtered. Anhydrous DCM (10 mL) and *p*-toluenesulfonic acid monohydrate (870 mg, 4.57 mmol) were added and the mixture was refluxed for 20 h under nitrogen then concentrated. The resulting yellow oil (750 mg) and triethylamine (1.41 mL, 10.1 mmol) were dissolved in anhydrous DCM (10 mL) and the solution was cooled to 0°C. Tosyl chloride (773 mg, 4.05 mmol) in anhydrous DCM (10 mL) was added and the mixture was stirred and allowed to warm up to room temperature overnight. The volatiles were removed *in vacuo* and a yellow oil was obtained which was purified by column chromatography using a gradient of hexane:EtOAc 95:5 to 75:25. Homoallylamine **1-73** was obtained as a colourless crystalline solid, 471 mg (1.58 mmol). Yield: 47% (¹H NMR (396 MHz, CDCl₃) δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 5.64 (ddt, $J = 17.4, 10.3, 7.2$ Hz, 1H), 5.21 – 5.04 (m, 3H), 4.04 – 3.92 (m, 3H), 2.49 – 2.44 (m, 2H), 2.41 (s, 3H), 1.12 (t, $J = 7.1$ Hz, 3H).⁶

⁵ Spectrum in accordance with: Bien, S.; Gillon, A.; Kohen, S. *J. C. S. Perkin I.* **1976**, 489.

⁶ Spectrum in accordance with: Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami M. *Angew. Chem. Intl. Ed.* **2013**, 52, 3883.

2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-tosyl-1,2,3,4-tetrahydropyridine (1-76): In a Fischer-Porter flask **1-62** (4.00 g, 10.4 mmol), Rh₂(OAc)₄ (46.1 mg, 0.104 mmol), BIPHEPHOS (164.5 mg, 0.209 mmol) were slurried in anhydrous toluene (110 mL). The flask was charged with 60 psi of CO:H₂ 1:1 and heated to 85°C for 64 h, then cooled and depressurized. Solvent was evaporated, and the residue was purified by column chromatography using hexane: EtOAc 95:5. **1-76** was obtained as a yellow oil, 3.61 g (9.15 mmol), yield: 88%.

¹H NMR (396 MHz, CDCl₃) δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 2H), 6.59 (d, *J* = 8.2 Hz, 1H), 5.09 – 4.99 (m, 1H), 4.11 – 3.91 (m, 1H), 3.84 – 3.65 (m, 2H), 2.41 (s, 3H), 2.03 – 1.71 (m, 3H), 1.61 – 1.48 (m, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.3, 136.1, 129.6 (2C), 127.0 (2C), 123.6, 109.4, 59.9, 50.2, 34.7, 25.9 (3C), 23.0, 21.5, 18.2, 17.3, -5.2, -5.3; FTIR (neat, cm⁻¹) *v*_{max} 1643, 1344, 1006; MS (ESI+) *m/z* 396 (MH⁺, 36), 418 (MNa⁺, 100); HRMS calcd for C₂₀H₃₄NO₃SSi (MH⁺) 396.2029; found: 396.2023.

When the synthesis of **1-76** was performed with a lower catalyst loading (0.1 mol%), **1-75** was obtained: ¹H NMR (396 MHz, CDCl₃) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.48 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.84 (tdd, *J* = 8.3, 4.3, 2.3 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.47 (s, 1H), 2.42 (s, 3H), 2.33 – 2.20 (m, 1H), 1.94 (dddd, *J* = 13.8, 8.1, 5.8, 4.3 Hz, 2H), 1.79 (d, *J* = 13.5 Hz, 1H), 1.66 (d, *J* = 13.5 Hz, 1H), 1.37 – 1.15 (m, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

2-(4-methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydropyridine (1-77): In a Fischer-Porter flask **1-64** (5.3 g, 16.01 mmol), Rh₂OAc₄ (7.1 mg, 0.016 mmol), BIPHEPHOS (25.2 mg, 0.032 mmol) were slurried in toluene (150 mL). The flask was charged 0 psi of CO:H₂ 1:1 and heated to 85°C for 40 h than cooled and depressurized. Solvent was evaporated, and the residue was triturated with diethyl ether on a filter than dried by suction. **1-77** was obtained as an off-white

solid, 4.28 g (12.31 mmol), yield: 77%. (Alternatively, column chromatography can be used (hexane: EtOAc 85:15), which delivers yields >90%).

^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 8.5 Hz, 2H), 5.14 – 5.09 (m, 1H), 5.06 – 4.99 (m, 1H), 3.77 (s, 3H), 2.41 (s, 3H), 1.91 – 1.82 (m, 1H), 1.81 – 1.71 (m, 1H), 1.70 – 1.54 (m, 1H), 1.46 – 1.34 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.6, 143.5, 136.3, 132.4, 129.7 (2C), 127.1 (2C), 127.0 (2C), 124.5, 113.7 (2C), 108.6, 55.4, 55.3, 26.2, 21.6, 16.9; FTIR (nujol, cm^{-1}) ν_{max} 1645, 1157; MS (ESI+) m/z 344 (MH^+ , 100), 366 (MH^+ , 91); HRMS calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_3\text{S}$ (MH^+) 344.1320; found: 344.1326; mp: 120-122 °C.

Ethyl 1-tosyl-1,2,3,4-tetrahydropyridine-2-carboxylate (1-78): In a Fischer-Porter flask **1-73** (405 mg, 1.36 mmol), Rh_2OAc_4 (3.0 mg, 0.006 mmol), BIPHEPHOS (10.7 mg, 0.013 mmol) were slurried in toluene (13 mL). The flask was charged with 60 psi $\text{CO}:\text{H}_2$ 1:1 and heated to 85°C for 22 h, then cooled and depressurized. Solvent was evaporated, and the residue was purified by column chromatography using hexane: EtOAc 90:10. **1-78** was obtained as a colourless solid, 379 mg (1.22 mmol), yield: 89%.

^1H NMR (396 MHz, CDCl_3) δ 7.68 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 9.2 Hz, 1H), 5.05 – 4.92 (m, 1H), 4.74 – 4.61 (m, 1H), 4.20 – 4.00 (m, 2H), 2.41 (s, 3H), 2.25 – 2.12 (m, 1H), 1.93 – 1.83 (m, 2H), 1.51 – 1.38 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 143.8, 136.0, 129.7 (2C), 126.9 (2C), 123.7, 107.2, 61.4, 54.7, 23.0, 21.4, 18.0, 14.0; FTIR (nujol, cm^{-1}) ν_{max} 1749, 1168; MS (ESI+) m/z 310 (MH^+ , 100), 332 (MNa^+ , 22); HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_4\text{S}$ (MH^+) 330.1113; found: 330.1110; mp: 75-77 °C.

N-(1-(4-methoxyphenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1-84): Activated Zn (1.21 g, 18.7 mmol) was slurried in anhydrous THF (30 mL) and propargyl bromide (80 w/w%

solution in toluene, 1.67 mL, 15 mmol) was added at room temperature. The mixture was stirred for 2 h, then it was added to a chilled solution of **1-63** (1.36 g, 4.7 mmol) in anhydrous THF (15 mL). The mixture was warmed up to room temperature overnight, then quenched with sat. aq. NH₄Cl solution and extracted three times with ether. The combined organic layers were washed with water and brine, then dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1 to 6:4. **1-84** was obtained as an off-white solid, 1.28 g (3.89 mmol), yield: 82%. (¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.44 (q, *J* = 6.2 Hz, 1H), 3.76 (s, 3H), 2.62 (dd, *J* = 6.1, 2.6 Hz, 2H), 2.39 (s, 3H), 1.98 (t, *J* = 2.6 Hz, 1H).⁷

2-(4-methoxyphenyl)-1-tosyl-2,3-dihydro-1H-pyrrole (1-85): A mixture of **1-84** (1.1 g, 3.34 mmol) and silver acetate (111 mg, 0.67 mmol) in anhydrous DCE (25 ml) was heated to 70°C for 7 hours (covered with aluminium foil). The mixture was cooled and filtered through Celite and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1 to 4:6. **1-85** was obtained as a colourless solid, 0.98 g (2.97 mmol), yield: 89%.

¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.51 (dt, *J* = 4.3, 2.1 Hz, 1H), 5.11 (dt, *J* = 4.9, 2.5 Hz, 1H), 4.68 (dd, *J* = 10.7, 6.2 Hz, 1H), 3.79 (s, 3H), 2.96 – 2.82 (m, 1H), 2.48 (ddd, *J* = 6.3, 2.7, 2.0 Hz, 1H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 143.7, 135.0, 134.3, 130.9, 129.7 (2C), 127.8 (2C), 127.7 (2C), 114.1 (2C), 110.1, 62.8, 55.4, 40.8, 21.7; FTIR (nujol, cm⁻¹

⁷ Spectrum in accordance with: Shu, C.; Liu, M.; Wang, S.; Li, L.; Ye, L. *J. Org. Chem.*, **2013**, 78, 3292.

¹) $\nu_{\max}$ 1336, 1168; MS (ESI+) m/z 330 (MH⁺, 100), 352 (MNa⁺, 73); HRMS calcd for C₁₈H₂₀NO₃S (MH⁺) 330.1164; found: 330.1164; mp: 114-115°C.

3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-tosyl-2-azabicyclo[4.1.0]heptane (1-86): To a solution of **1-76** (1.00 g, 2.53 mmol) and CH₂I₂ (2.31 mL, 30.38 mmol) in anhydrous toluene (63 mL) Et₂Zn (1 M solution in hexanes, 15.2 mL, 15.2 mmol) was added at 0°C under nitrogen. The mixture was stirred at 0°C for 60 h, and sat. aq. NH₄Cl (40 mL) was added. The mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ than filtered and concentrated. The crude product was purified by column chromatography using hexane: EtOAc 9:1. **1-86** was obtained as a colourless oil, 792 mg (1.93 mmol), yield: 76%.

¹H NMR (396 MHz, CDCl₃) δ 7.72 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 3.87 – 3.79 (m, 1H), 3.70 (t, J = 6.9 Hz, 2H), 2.83 – 2.74 (m, 1H), 2.41 (s, 3H), 1.97 – 1.69 (m, 2H), 1.68 – 1.51 (m, 2H), 1.50 – 1.38 (m, 1H), 1.23 – 1.11 (m, 1H), 1.11 – 0.96 (m, 1H), 0.90 (s, 9H), 0.58 (dt, J = 9.5, 6.0 Hz, 1H), 0.08 (s, 3H), 0.07 (s, 3H), -0.08 (td, J = 6.2, 3.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 142.9, 138.2, 129.5 (2C), 127.4 (2C), 60.8, 48.6, 35.0, 26.2, 26.0 (3C), 24.3, 21.6, 18.4, 14.7, 10.1, 8.6, -5.1, -5.2; FTIR (neat, cm⁻¹) $\nu_{\max}$ 1342, 1006, 732; MS (ESI+) m/z 410 (MH⁺, 100), 432 (MNa⁺, 40); HRMS calcd for C₂₁H₃₆NO₃SSi (MH⁺) 410.2185; found: 410.2189.

3-(4-methoxyphenyl)-2-tosyl-2-azabicyclo[4.1.0]heptane (1-87): To a solution of **1-77** (3.43 g, 10.0 mmol) and CH₂I₂ (9.12 mL, 120 mmol) in toluene (250 mL) Et₂Zn (1 M solution in hexanes, 60 mL, 60 mmol) was added at 0°C under nitrogen. The mixture was stirred at 0°C for 60 h, then sat. aq. NH₄Cl was added and extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO₄ than filtered and concentrated. The crude

product was purified by column chromatography using hexane:EtOAc 6:1 to 5:1. **1-87** was obtained as a colourless solid, 3.13 g (8.76 mmol), yield: 87%.

^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, J = 8.0 Hz, 2H), 7.32 – 7.18 (m, 4H), 6.86 (d, J = 8.5 Hz, 2H), 5.00 – 4.95 (m, 1H), 3.80 (s, 3H), 3.10 – 3.01 (m, 1H), 2.42 (s, 3H), 1.93 – 1.78 (m, 1H), 1.54 – 1.35 (m, 3H), 1.20 – 1.04 (m, 1H), 0.65 (dt, J = 9.4, 6.0 Hz, 1H), 0.10 (td, J = 6.4, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.5, 143.2, 137.8, 132.6, 129.5 (2C), 127.6 (2C), 127.5 (2C), 113.9 (2C), 55.4, 54.0, 21.7, 14.8, 10.9, 9.2; FTIR (nujol, cm^{-1}) ν_{max} 1157, 721; MS (ESI+) m/z 358 (MH^+ , 64), 380 (MNa^+ , 100); HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S}$ (MH^+) 358.1477; found: 358.1465; mp: 104-107 °C.

Ethyl 2-tosyl-2-azabicyclo[4.1.0]heptane-3-carboxylate (1-88): To a solution of **1-78** (831 mg, 2.69 mmol) and CH_2I_2 (2.45 mL, 32.27 mmol) in toluene (67 mL) Et_2Zn (1 M solution in hexanes, 16.1 mL, 16.13 mmol) was added at 0°C under nitrogen. The mixture was stirred at 0°C for 60 h, then sat. aq. NH_4Cl was added than extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 than filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15 to 80:20. **1-88** was obtained as a colourless oil, which slowly crystallized. 740 mg (2.29 mmol), yield: 79%. Product was obtained as a 1:1 mixture of diastereomers.

^1H NMR (396 MHz, CDCl_3) δ 7.78 (d, J = 8.3 Hz, 2H dia1), 7.75 (d, J = 8.3 Hz, 2H dia2), 7.29 (m, 2H dia1, 2H dia2), 4.51 – 4.47 (m, 1H dia2), 4.45 (dd, J = 6.3, 2.8 Hz, 1H dia1), 4.26 – 4.01 (m, 2H dia1, 2H dia2), 2.98 – 2.90 (m, 1H dia2), 2.72 (ddd, J = 8.8, 6.2, 3.8 Hz, 1H dia1), 2.43 (s, 3H dia1), 2.42 (s, 3H dia2) 2.00 (m, 2H dia2), 1.96 – 1.87 (m, 1H dia1), 1.75 (tdd, J = 13.8, 6.3, 3.7 Hz, 1H dia1), 1.66 (dt, J = 7.8, 3.3 Hz, 1H dia1), 1.50 – 1.37 (m, 1H dia2), 1.23 (m, 3H dia1, 3H dia2), 1.19 – 1.03 (m, 2H dia1, 2H dia2), 0.73 (dt, J = 9.5, 5.9 Hz, 1H dia2), 0.63 (dt, J = 9.0, 6.0 Hz, 1H dia1), 0.35 (td, J = 5.8, 3.8 Hz, 1H dia1), 0.16 (ddd, J = 7.0, 5.9,

3.4 Hz, 1H dia2). ^{13}C NMR (100 MHz, CDCl_3) δ 172.3, 172.2, 143.4, 137.4, 136.4, 129.6, 129.3, 128.2, 127.5, 61.4, 61.3, 55.2, 53.9, 27.7, 26.2, 26.1, 24.9, 21.8, 21.7, 18.3, 16.8, 14.4, 14.3, 13.4, 11.2, 11.1, 10.1; FTIR (neat, cm^{-1}) ν_{max} 1747, 13366, 746; MS (ESI+) m/z 324 (MH^+ , 100), 346 (MH^+ , 48); HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{S}$ (MH^+) 324.1270; found: 324.1267.

3-(4-methoxyphenyl)-2-tosyl-2-azabicyclo[3.1.0]hexane (1-89): To a solution of **1-85** (950 mg, 2.88 mmol) and CH_2I_2 (2.63 mL, 34.65 mmol) in anhydrous toluene (71 mL) Et_2Zn (1 M solution in hexanes, 17.3 mL, 17.32 mmol) was added at 0°C under nitrogen. The mixture was stirred at 0°C for 69 h, then sat. aq. NH_4Cl was added and extracted three times with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 than filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1 to 2:1. **1-89** was obtained as an off-white solid. 660 mg (1.92 mmol), yield: 67%.

^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 3.85 – 3.69 (m, 4H), 3.56 (td, $J = 6.1, 2.5$ Hz, 1H), 2.42 (s, 3H), 2.28 (dd, $J = 13.0, 7.7$ Hz, 1H), 2.15 – 1.98 (m, 1H), 1.56 – 1.46 (m, 1H), 0.40 (dt, $J = 8.5, 6.2$ Hz, 1H), 0.18 – 0.11 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 143.7, 133.7, 133.3, 129.4 (2C), 128.8 (2C), 128.2 (2C), 113.9 (2C), 61.1, 55.4, 39.7, 38.9, 21.8, 13.0, 8.1; FTIR (nujol, cm^{-1}) ν_{max} 1136, 1168, 721; MS (ESI+) m/z 344 (MH^+ , 48), 366 (MNa^+ , 100); HRMS calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_3\text{S}$ (MH^+) 344.1320; found: 344.1301. mp: $120\text{--}122^\circ\text{C}$ (decomp).

(1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)methanol (1-90) : **1-78** (220 mg, 0.712 mmol) was dissolved in diethyl ether and cooled to 0°C under a stream of nitrogen. LiAlH_4 (32.5 mg, 0.854 mmol) was added portion wise. The reaction was quenched by the addition of water after 25 min. MgSO_4 was added, and the mixture was stirred for 30 min, then filtered and concentrated. **1-90** was obtained as a colourless oil, 188 mg (0.704 mmol), 99 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.68 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 7.6 Hz, 1H), 5.09 – 5.01 (m, 1H), 4.05 – 3.98 (m, 1H), 3.71 (dd, J = 11.0, 7.4 Hz, 1H), 3.49 (dd, J = 11.0, 6.7 Hz, 1H), 2.85 (brs, 1H), 2.41 (s, 3H), 1.99 – 1.85 (m, 1H), 1.84 – 1.71 (m, 2H), 1.00 – 0.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.8, 135.4, 129.8 (2C), 126.9 (2C), 123.2, 109.1, 61.8, 54.3, 21.5, 20.2, 17.2; FTIR (neat, cm^{-1}) ν_{max} 3305, 1457, 1336, 1165; MS (ESI+) m/z 268 (MH^+ , 100), 290 (MNa^+ , 47); HRMS calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{S}$ (MH^+) 268.1007; found: 268.1016.

(2-*tosyl-2-azabicyclo[4.1.0]heptan-3-yl*)methanol (**1-91**): **1-90** (180 mg, 0.674 mmol) and CH_2I_2 (0.615 mL, 8.089 mmol) were dissolved in dry toluene (16.5 mL) under nitrogen. After cooling to 0 °C, a Et_2Zn (1M solution in hexanes, 4 mL, 4.044 mmol) was added. Reaction was stirred at 0 °C for 60 h, then quenched with sat. aq. NH_4Cl solution. The mixture was extracted three times with EtOAc. The combined organics were dried, filtered and concentrated. The crude product was purified by column chromatography using a gradient of hexanes:EtOAc 3:1 to 1:1. **1-91** was obtained as a colourless oil, 40 mg (0.142 mmol), 21% yield.

^1H NMR (396 MHz, CDCl_3) δ 7.76 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.84 – 3.72 (m, 2H), 3.61 – 3.46 (m, 1H), 2.92 (ddd, J = 8.4, 6.3, 3.6 Hz, 1H), 2.49 – 2.30 (m, 4H), 1.82 – 1.67 (m, 1H), 1.66 – 1.48 (m, 2H), 1.30 – 1.18 (m, 1H), 1.10 – 0.96 (m, 1H), 0.62 (dt, J = 6.0, 3.8 Hz, 1H), -0.05 (td, J = 6.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.5, 137.4, 129.7 (2C), 127.5 (2C), 62.7, 53.0, 26.5, 21.7, 21.6, 15.1, 10.6, 8.7; MS (ESI+) m/z 282 (MH^+ , 100); HRMS calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$) 282.1164; found: 282.1154.

2-(2-*tosyl-2-azabicyclo[4.1.0]heptan-3-yl*)ethan-1-ol (**1-92**): A solution of **1-86** (2.50 g, 6.1 mmol) in THF (198 mL) was cooled to 0 °C and TBAF $\cdot$ 3H $_2$ O (3.08 g, 9.7 mmol) was added and the mixture was stirred for 1 hour, then warmed up to room temperature over 2 hours. The reaction was quenched with brine and extracted four times with EtOAc. The combined organic

layers were dried over anhydrous MgSO_4 than filtered and concentrated. The crude product was purified by column chromatography using hexane: EtOAc 9:1 to 1:1. **1-92** was obtained as a colourless oil, 1.71 g (5.78 mmol), yield: 95%.

^1H NMR (396 MHz, CDCl_3) δ 7.74 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 4.02 – 3.86 (m, 2H), 3.80 – 3.67 (m, 1H), 3.12 – 3.01 (m, 1H), 2.87 – 2.79 (m, 1H), 2.43 (s, 3H), 1.95 – 1.72 (m, 2H), 1.60 – 1.52 (m, 1H), 1.51 – 1.42 (m, 1H), 1.40 – 1.32 (m, 1H), 1.25 – 1.12 (m, 1H), 1.10 – 0.96 (m, 1H), 0.55 (dt, $J = 9.5, 6.0$ Hz, 1H), -0.19 (td, $J = 6.3, 3.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.4, 137.4, 129.6 (2C), 127.2 (2C), 58.6, 47.6, 34.0, 25.9, 24.6, 21.5, 14.5, 9.9, 7.6; FTIR (neat, cm^{-1}) ν_{max} 3523, 1336, 1161, 742; MS (ESI+) m/z 296 (MH^+ , 100), 318 (MNa^+ , 39); HRMS calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_3\text{S}$ (MH^+) 296.1320; found: 296.1326.

3-(2-(allyloxy)ethyl)-2-tosyl-2-azabicyclo[4.1.0]heptane (1-93): A mixture of **1-92** (500 mg, 1.69 mmol), allyl bromide (0.66 mL, 7.62 mmol), NaOH (303 mg, 7.62 mmol) and tetra-*n*-butylammonium bromide (163.5 mg, 0.51 mmol) in toluene (5 mL) was heated to 50°C for 23 h. The mixture was filtered and the filtrate was concentrated. The crude product was purified by column chromatography using hexane: EtOAc 9:1. **1-93** was obtained as a colourless oil, 453 mg (1.35 mmol), yield: 80%.

^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 5.95 (ddt, $J = 17.3, 11.0, 5.7$ Hz, 1H), 5.29 (d, $J = 17.3$ Hz, 1H), 5.18 (d, $J = 11.0$ Hz, 1H), 4.08 – 3.95 (m, 2H), 3.93 – 3.87 (m, 1H), 3.63 – 3.53 (m, 2H), 2.84 – 2.77 (m, 1H), 2.41 (s, 3H), 2.02 – 1.92 (m, 1H), 1.88 – 1.76 (m, 1H), 1.66 – 1.50 (m, 2H), 1.47 – 1.37 (m, 1H), 1.23 – 1.13 (m, 1H), 1.08 – 0.97 (m, 1H), 0.55 (dt, $J = 9.5, 6.0$ Hz, 1H), -0.15 (td, $J = 6.3, 3.8$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 142.8, 137.9, 135.0, 129.2 (2C), 127.1 (2C), 116.4, 71.7, 64.4, 48.4, 32.0, 25.8, 24.3, 21.3, 14.4, 9.8, 8.0; FTIR (neat, cm^{-1}) ν_{max} 1641, 1450, 1085, 920; MS (ESI+)

m/z 336 (MH^+ , 100), 358 (MNa^+ , 44); HRMS calcd for $C_{18}H_{26}NO_3S$ (MH^+) 336.1633; found: 336.1629.

2-(5-methyl-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethan-1-ol (1-94): **1-92** (75 mg, 0.25 mmol) and $(EtCN)_4Pt(OTf)_2$ (18 mg, 0.025 mmol) were heated to reflux under nitrogen in toluene (2.2 mL) for 14 h. The mixture was cooled, concentrated and the crude product was purified by column chromatography using a gradient of hexane: EtOAc 85:15 to 80:20. **1-94** was obtained as a colourless oil, 42 mg (0.14 mmol), yield: 56%.

1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.36 (s, 1H), 4.22 – 3.98 (m, 1H), 3.88 (t, J = 11.4 Hz, 1H), 3.71 – 3.60 (3, 1H), 3.00 – 2.89 (m, 1H), 2.41 (s, 3H), 1.97 – 1.67 (m, 1H), 1.67 – 1.51 (m, 5H), 1.49 – 1.26 (m, 2H), 0.97 – 0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 135.5, 129.9 (2C), 127.1 (2C), 119.6, 117.5, 58.4, 48.4, 34.0, 23.8, 23.0, 21.7, 21.0; FTIR (neat, cm^{-1}) ν_{max} 3417, 1635, 1448, 1161; MS (ESI+) m/z 296 (MH^+ , 100), 318 (MNa^+ , 94); HRMS calcd for $C_{15}H_{22}NO_3S$ (MH^+) 296.1320; found: 296.1321.

2-(4-methoxyphenyl)-5-methyl-1-tosyl-1,2,3,4-tetrahydropyridine (1-95): A mixture of **1-87** (500 mg, 1.4 mmol) and $(EtCN)_4Pt(OTf)_2$ (100 mg, 0.14 mmol) was heated to 80°C under nitrogen in toluene (15 mL) for 14 h. The mixture was cooled and filtered through Celite then concentrated. The resulting black oil was purified by column chromatography using a gradient of hexane:EtOAc 95:5 to 90:10. **1-95** was obtained as a yellow solid, 252 mg (0.705 mmol), yield: 50%.

1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 6.63 (s, 1H), 5.09 – 5.05 (m, 1H), 3.76 (s, 3H), 2.39 (s, 3H), 1.91 – 1.82 (m, 1H), 1.66 – 1.53 (m, 5H), 1.41 – 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 143.1, 136.1, 132.2, 129.5 (2C), 126.9 (2C), 126.8 (2C), 118.5, 117.8, 113.5

(2C), 55.1, 54.3, 25.8, 22.2, 21.4, 20.1; FTIR (nujol, cm^{-1}) ν_{max} 1635, 1166; MS (ESI+) m/z 358 (MH^+ , 100), 380 (MNa^+ , 98); HRMS calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3\text{S}$ (MH^+) 358.1477; found: 358.1479; mp: 105-107 °C.

Ethyl 5-methyl-1-tosyl-1,2,3,4-tetrahydropyridine-2-carboxylate (1-96): A mixture of **1-88** (150 mg, 0.46 mmol) and Zeise's dimer (27.3 mg, 0.046 mmol) were heated to reflux under nitrogen in anhydrous toluene (4.5 mL) for 15 h. The mixture was cooled and concentrated and the crude product was purified by column chromatography using hexane:EtOAc 90:10. **1-96** was obtained as a colourless oil which slowly crystallized, 107 mg (0.33 mmol), yield: 71%.

^1H NMR δ 7.68 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 4.64 (dd, J = 4.4, 3.4 Hz, 1H), 4.12 (q, J = 8.0 Hz, 1H), 2.42 (s, 3H), 2.16 (dddd, J = 13.5, 5.9, 2.8, 1.9 Hz, 1H), 1.92 – 1.79 (m, 1H), 1.77 – 1.73 (m, 1H), 1.73 – 1.68 (m, 1H), 1.64 (s, 3H), 1.49 – 1.38 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz CDCl_3) δ 170.3, 143.8, 136.4, 129.9, 127.3, 118.3, 116.7, 61.7, 54.4, 23.7, 23.4, 21.8, 21.0, 14.3; FTIR (nujol, cm^{-1}) ν_{max} 1749, 1168; MS (ESI+) m/z 324 (MH^+ , 86), 346 (MNa^+ , 100); HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{S}$ (MH^+) 324.1270; found: 324.1275;

3-(4-methoxyphenyl)-6-methyl-2-tosyl-2-azabicyclo[4.1.0]heptane (1-104): To a solution of **1-95** (765 mg, 2.14 mmol) and CH_2ICl (1.25 ml, 17.1 mmol) in dry DCE (76 ml) at 0°C was added Et_2Zn (8.27 mmol) and stirred for 60 hours. The mixture was quenched with sat. aq. NH_4Cl and extracted with CHCl_3 . The organic layer was dried over anhydrous MgSO_4 than filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1 to 3:1. **1-104** was obtained as a colourless foam. 535 mg (1.45 mmol), yield: 68%.

^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 4.98 (t, J = 3.5 Hz, 1H), 3.79 (s, 3H), 2.86 (dd, J = 6.3,

3.6 Hz, 1H), 2.40 (s, 3H), 1.86 – 1.77 (m, 1H), 1.51 – 1.41 (m, 1H), 1.39 – 1.18 (m, 2H), 0.96 (s, 3H), 0.49 (t, $J = 6.0$ Hz, 1H), 0.20 (dd, $J = 5.5, 3.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.4, 143.1, 137.6, 132.7, 129.5 (2C), 127.4 (2C), 127.3 (2C), 113.8 (2C), 55.3, 54.2, 35.4, 27.5, 25.6, 22.0, 21.6, 16.7, 16.5; FTIR (nujol, cm^{-1}) ν_{max} 1614, 1342, 742; MS (ESI+) m/z 372 (MH^+ , 100), 394 (MNa^+ , 28), 765 (2MNa^+ , 65); HRMS calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3\text{S}$ (MH^+) 372.1633; found: 372.1626.

In case the synthesis of **1-104** was ran with traces of oxygen present, a Prins reaction product was observed:

7-(4-methoxyphenyl)-4a-methyl-8-tosylhexahydro-4H-[1,3]dioxino[4,5-b]pyridine (1-121) : ^1H NMR (396 MHz, CDCl_3) δ 7.05 (d, $J = 8.3$ Hz, 2H), 6.93 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.40 (d, $J = 8.8$ Hz, 2H), 5.35 (s, 1H), 5.13 (d, $J = 7.3$ Hz, 1H), 4.81 (d, $J = 6.4$ Hz, 1H), 4.34 (dd, $J = 12.1, 3.6$ Hz, 1H), 3.67 (s, 3H), 3.62 (d, $J = 12.3$ Hz, 1H), 3.49 (d, $J = 11.4$ Hz, 1H), 2.49 (td, $J = 13.8, 4.6$ Hz, 1H), 2.28 (s, 3H), 1.97 (tdd, $J = 14.1, 12.4, 4.5$ Hz, 1H), 1.65 (ddd, $J = 14.1, 6.9, 4.2$ Hz, 1H), 1.23 – 1.11 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 142.5, 138.8, 131.1, 130.8, 128.8, 127.7, 112.8, 93.3, 89.2, 76.9, 58.0, 55.3, 34.6, 31.7, 26.9, 21.6, 18.8; FTIR (nujol, cm^{-1}) ν_{max} 1629, 1159; MS (ESI+) m/z 418 (MH^+ , 20), 440 (MNa^+ , 38), 857 (2MNa^+ , 100) ; HRMS calcd. for $\text{C}_{22}\text{H}_{28}\text{NO}_5\text{S}$ 418.1688, found 418.1699; mp 110-111 °C.

6-(4-methoxyphenyl)-2-methyl-3-methylene-1-tosylpiperidine (1-106): A solution of **1-104** (37 mg, 0.1 mmol) and Zeise's dimer (3.9 mg, 0.01 mmol) in dry DCE (1.5 ml) was heated to reflux overnight than filtered through celite and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1. **1-106** was obtained as a yellow solid. 7.4 mg (0.02 mmol), yield: 20%.

NMR (396 MHz, CDCl₃) δ 7.72 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.10 – 5.01 (m, 1H), 4.75 (q, J = 7.2 Hz, 1H), 4.66 (s, 1H), 4.59 (s, 1H), 3.81 (s, 3H), 2.42 (s, 5H), 2.27 – 2.18 (m, 1H), 1.88 (dt, J = 14.2, 4.6 Hz, 1H), 1.05 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.7, 145.9, 143.1, 129.7 (2C), 128.4 (2C), 127.4 (2C), 113.8 (2C), 109.5, 56.45, 55.5, 53.4, 26.9, 25.3, 24.4, 21.7. FTIR (nujol, cm⁻¹) ν_{max} 1639, 1156; MS (ESI+) m/z 372 (MH⁺, 100), 394 (MNa+35; HRMS calcd. For C₂₁H₂₆NO₃S 372.1633, found 372.1649; mp: 127 -129 °C.

1.10 References

1. Anslyn, E. V.; Dougherty, D. A., In *Modern Physical Organic Chemistry*, University Science Books: Sausalito, 2005.
2. Newham, J., *Chem. Rev.* **1963**, 63, 123.
3. Freund, A., *J. Prakt. Chem.* **1882**, 26, 367.
4. Perkin, W. H., *J. Chem. Soc.* **1929**, 1347.
5. Willstatter, R.; Bruce, J., *Ber. Dtch. Chem. Ges.* **1907**, 40, 4456.
6. Wong, H. N. C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T., *Chem. Rev.* **1989**, 89, 165.
7. De Simone, F.; Gertsch, J.; Waser, J., *Angew. Chem.* **2010**, 122, 5903.
8. Boeckman, R. K., Jr; Charette, A. B.; Asberom, T.; Johnston, B. H., *J. Am. Chem. Soc.* **1991**, 113, 5337.
9. Lang, R. W., Djerassi, C., *Helv. Chim. Acta* **1982**, 65, 407.
10. Danishefsy, S.; Singh, R.K., *J. Am. Chem. Soc.* **1975**, 97, 3239.
11. Reissig, H.; Zimmer, R.; *Chem. Rev.* **2003**, 103, 1151.
12. Ramana, C. V.; Murali, R.; Nagarajan, M., *J. Org. Chem.* **1997**, 62, 7694.
13. Scott, R. W.; Heathcock, C. H., *Carbohydr. Res.* **1996**, 291, 205.
14. Ryu, I.; Ando, M.; Ogawa, A.; Murai, S.; Sonoda, N., *J. Am. Chem. Soc.* **1983**, 105, 7192.
15. Sun, R.; Zhang, D.; Shi, M., *Synlett* **2014**, 25, 2293.
16. Mancey, N. C.; Sandon, N.; Auvinet, A.; Butlin, R. J.; Czechtizky, W.; Harrity, J. P. A., *Chem. Comm.* **2011**, 47, 9804
17. Hoberg, J. O.; Claffey, D. J., *Tet. Lett.* **1996**, 37, 2533.
18. Hoberg, J. O., *J. Org. Chem.* **1997**, 62, 6615.
19. Volger, H. C.; Hogeveen, H.; Gaasbeek, M. M. P., *J. Am. Chem. Soc.* **1969**, 91, 2137.

20. Volger, H. C.; Hogeveen, H.; Gaasbeek, M. M. P., *J. Am. Chem. Soc.* **1969**, *91*, 218.
21. (a) Shimzu, I.; Ohashi, Y.; Tsuji, J., *Tet. Lett.* **1985**, *26*, 3825; (b) Hirata, G.; Onodera, G.; Kimura, M., *Synlett* **2014**, *25*, 2306.
22. Tomobe, R.; Iwamoto, T.; Kurahasi, T.; Matsubara, S., *Synlett* **2014**, *25*, 2281.
23. Shaw, M.H.; Meliknova, E.Y.; Kloer, D.P.; Whittingham, W.G.; Bower, J.F., *J. Am. Chem. Soc.* **2013**, *135*, 4992.
24. Tipper, C. F. H., *J. Chem. Soc.* **1955**, 2045.
25. Jennings, P. W.; Johnson, L. L., *Chem. Rev.* **1994**, *94*, 2241.
26. Beyer, J.; Madsen, R. J., *J. Am. Chem. Soc.* **1998**, *120*, 12137.
27. (a) Doyle, M. P.; van Leusen, D., *J. Org. Chem.* **1982**, *47*, 5326; (b) Ikura, K.; Ryu, I.; Kambe, N.; Sonoda, N., *J. Am. Chem. Soc.* **1992**, *114*, 1520; (c) Hoberg, J. O.; Jennings, P. W., *Organometallics* **1996**, *15*, 3902.
28. Beyer, J.; Skraanderup, P. R.; Madsen, R. J., *J. Am. Chem. Soc.* **2000**, *122*, 9575.
29. Ikura, K.; Ryu, I.; Ogawa, A.; Sonoda, N.; Harada, S.; Kasai, N., *Organometallics* **1991**, *10*, 528.
30. Sugimura, T.; Futagawa, T.; Ryu, I.; Tai, A., *Journal of the Chem. Soc. Chem. Comm.* **1992**, 324.
31. Ikura, K.; Ryu, I.; Ogawa, A.; Kambe, N.; Sonoda, N., *Tet. Lett.* **1989**, *30*, 6887.
32. Kasinathan, S. PhD. Thesis, Nanyang Technological University 2013.
33. Spangenberg, T.; Airiau, E.; Thuong, M. B. T.; Donnard, M.; Billet, M.; Mann, A., *Synlett* **2008**, 2859.
34. Dewey, M. R. Ph.D. Thesis, Nanyang Technological University, 2009.
35. Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.* **1999**, *64*, 4537.
36. Marshall, J. A.; Van Devender, E. A., *J. Org. Chem.* **2001**, *66*, 8037.
37. Schmid, P.; Veenstra, S. J., *Tet. Lett.* **1997**, *38*, 997.

38. Kulesza, A.; Jurczak, J., *Synthesis* **2003**, 2110.
39. Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G., *Synthesis* **1972**, 544.
40. Bien, S.; Gillon, A.; Kohen, S., *J. Chem. Soc. Per. Trans. I.* **1976**, 489.
41. Pfister, J. R.; Wymann, W. E., *Synthesis* **1983**, 38.
42. Bates, R. W.; Kasinathan, S.; Straub, B. F., *J. Org. Chem.* **2011**, 76, 6844.
43. Bates, R. W.; Kasinathan, S., *Tetrahedron* **2013**, 69, 3088.
44. Bates, R. W.; Aslam, N. F. B. M.; Tang, C. H.; Simon, O., *Tetrahedron* **2014**, 70, 2143.
45. McDonald, F. E.; White, B. H., *Org. Syn.* **2004**, Coll. Vol. 10, 621.
46. Berry, M. B.; Craig, D., *Synlett* **1992**, 41.
47. Koh, W. M. L. BSc Thesis, Nanyang Technological University, 2013.
48. Pan, J.; Zhang, M.; Zhang, S., *Org. Biomol. Chem.* **2012**, 10, 1060.
49. Pattenden, L. C.; Adams, H.; Smith, S. A.; Harrity, J. P. A., *Tetrahedron* **2008**, 64, 2951.
50. Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V., *Tetrahedron* **1991**, 47, 1311.
51. Denmark, S. E.; Edwards, J. P., *J. Org. Chem.* **1991**, 56, 6974.
52. Maruoka, K.; Fukutani, Y.; Yamamoto, H., *J. Org. Chem.* **1985**, 50, 4414.
53. Furukawa, J.; Kawabata, N.; Nishimura, J., *Tet. Lett.* **1966**, 7, 3353.
54. Martinez, C.R.; Iverson, B.L., *Chem. Sci.* **2012**, 3, 3191.
55. Prins, H. J., *Chemisch Weekblad* **1919**, 1072.
56. (a) Arundale, E.; Mikeska, L. A., *Chem. Rev.* **1952**, 51, 505; (b) Adams, D. R.; Bhatnagar, S. P., *Synthesis* **1977**, 661; (c) Pastor, I. M.; Yus, M., *Curr. Org. Chem.* **2007**, 11, 925; (d) Pastor, I. M.; Yus, M., *Curr. Org. Chem.* **2012**, 16, 1277.
57. Smissman, E. E.; Schnettler, R. A.; Porthoghese, P. S., *J. Org. Chem.* **1965**, 30, 797.

58. Li, G.; Gu, Y.; Ding, Y.; Zhang, H.; Wang, J.; Gao, Q.; Yan, L.; Suo, J., *J. Mol. Cat. A: Chem.* **2004**.
59. Sreedhar, B.; Swapna, V.; Sridhar, C.; Saileela, D.; Sunitha, A., *Synth. Comm.* **2005**, 35, 1117.
60. Chandrasekhar, S.; Reddy, B. V. S., *Synlett* **1988**, 851.
61. Yadav, J. S.; Reddy, B. V. S.; Bhaishya, G., 5. *Green Chem.* **2003**, 264.
62. Bach, T.; Lobel, J., *Synthesis* **2002**, 2521.
63. Yadav, J. S.; Subba, B. V.; Reddy, A. V.; Gopal, H.; Kumar, G. G. K. S. N.; Madavi, C.; Kunwar, A. C., *Tet. Lett.* **2008**, 49, 4420.
64. (a) Wittig, G.; Wingler, F., *Chem. Ber.* **1967**, 97, 2146; (b) Blanchard, E. P.; Simmons, H. E., *J. Am. Chem. Soc.* **1964**, 86, 1337.

Chapter 2

The Total Synthesis of Lupin Alkaloids

2.1 Abstract

We report a stereodivergent enantioselective total synthesis for several Lupin alkaloids. Our strategy features an uncommon 6-*endo* aza-Michael cyclisation as the key step which allows us to access *cis* and *trans* 3,5-disubstituted piperidine rings in a stereodivergent fashion. The whole linear total synthesis is a combination of classical organic transformations and recent cross coupling methods. The chirality originates in this synthetic approach from a diastereoselective alkylation using Evans' oxazolidinone where our compound does not follow the Evans model, thus, making it, to the best of our knowledge, the first ever reported exception.

Several approaches are described for attempted total synthesis using a variety of cyclisation reactions which were unsuccessful, but yielded a series of interesting compounds and mechanistic insights to cyclisation chemistry.

2.2 Introduction

The Prins reaction discussed in Chapter 1.7 has inspired us to pursue the total synthesis of Lupin alkaloids. The formation of the dioxanopiperidine product under complete stereocontrol seemed to be suitable surrogate for a 3-hydroxymethylpiperidine scaffold, which is a common structural feature in almost all Lupin alkaloids. These alkaloids bear a 3,5-disubstituted piperidine core, which is a fundamental difference compared to the compounds investigated in Chapter 1, as in that case the substituent α to the piperidine nitrogen was in an axial position, while in this case the β substituent will be equatorial. This major difference would be expected to effect the diastereoselectivity of the Prins reaction, which was not a concern to us, as the Lupin alkaloid family contains both *cis* and *trans* 3,5-disubstituted piperidines.

2.3 Isolation and Biological activity

Plant extracts containing Lupin alkaloids have been studied for over 150 years. *Cytisine* in its pure form was first isolated by Husemann and Marme in 1862¹ and its correct structure was proposed in 1931 by Ing².

(+)-*Kuraramine* was isolated in 1981 from the flowers of *Sophora Flavescens* which mainly grows in Japan.³ Its structure was proposed correctly and it is believed to be a possible metabolite of (-)-*N*-methylcytisine.

Isokuraramine was isolated also from the flowers of *Sophora flavescens* 1982.⁴ Its structure was correctly proposed as *kuraramine* was already known, but the isolated material was not sufficient for optical rotation measurements. This was conformed later by several groups who have isolated isokuraramine from different Lupin plants.

The *jussiaeiine* family (A-D) was isolated in 2000 from *Ulex jussiaei* in Portugal.⁵ Their structure was considered unique at the time of isolation, as they possess a 2,6-disubstituted pyridine moiety instead of the usual 2-pyridone found in similar alkaloids.

There is no available data on the biological activity of the individual Lupin alkaloids of our interest, except for *cytisine*. The extracts of Lupin plants have been tested for the treatment of various conditions and diseases, i.e. gastric ulcer and have shown promising results.

Without doubt, the most interesting member of the Lupin alkaloid family is *cytisine*: the *British Medical Journal* calls it ‘The world’s oldest smoking cessation aid’.⁶ It is derived from the plant *Cytisus laburum* and known since 1818. As a smoking cessation aid, it was widely used by German and Russian soldiers during World War 2, and became an increasingly popular remedy in Eastern Europe. Early clinical trials were conducted in the 1960’s and 70’s in Eastern Europe, and the first thorough investigations took place in the early 2010’s. (-)-*Cytisine* acts as a neuronal nicotinic acetylcholine receptor (nAChR) agonist on several subtypes, either as a full or a partial agonist.⁷ As a result of receptor binding, dopamine is released, which causes a sensation of satisfaction in addicts, making *cytisine* a suitable tobacco substitute. Despite all the promising data, *cytisine* performed rather poorly *in vivo* due to its limited bioavailability.⁸ The poor absorption⁹ of *cytisine* and its low permeability on the blood-brain-barrier¹⁰ did not make it a suitable drug candidate, however it was subjected to several SAR studies, and analogs have been made and tested. This research done by Pfizer resulted in an FDA approved *cytisine*-inspired smoking cessation drug, *varenicline*.

Figure 59: Natural Product (*cytisine*, left) and the marketed drug (*varenicline*, right)

It has been also shown recently, that *cytisine*-containing extracts of *Sophora alopecuroides* are able to treat morphine withdrawal symptoms in mice.¹¹

Cytisine and its analogues are being continuously studied both as potential APIs as well as its synthetic chemistry applications such as ligands in asymmetric catalysis.¹²

2.4 Total Synthesis of Lupin Alkaloids: Literature Review

The total synthesis of *cytisine* has been reviewed by Stead and O'Brien in 2007.¹³ Since then, only two more approaches have been reported on *cytisine*. As for the other target alkaloids, one enantioselective approach exists, yielding the unnatural enantiomers.

Cytisine in its racemic form was first synthesised by van Tamelen in 1955¹⁴, shortly followed by Bohlmann¹⁵ and Govindachari¹⁶. After these pioneering approaches, nearly 50 years had to pass for another *cytisine* synthesis to be published. The discovery of *cytisine*'s biological significance drew attention from both academia and industry and resulted in several racemic and enantioselective total syntheses.

Although (-)-*cytisine* can be extracted from *Laburnum anagyroides* seeds in an economical way¹⁷, there is still a need for synthetic approaches to its biologically active core structure for drug discovery.

Before discussing the existing synthetic approaches, it has to be noted that enantiopure *cytisine* can be easily obtained from the racemic form via resolution with *d*-camphor-10-sulphonic acid, and this method has been described by van Tamelen.^{14b}

Besides the historical significance of van Tamelen's synthesis, it is also conceptually interesting. The piperidine ring is constructed using an *aza*-Michael cyclisation and the bridged scaffold of *cytisine* is accessed through an intramolecular nucleophilic substitution, which is a common feature of our synthesis as well.

Figure 60: van Tamelen's synthesis.

In van Tamelen's synthesis (Figure 60) a Mannich base undergoes an *aza*-Michael cyclisation, which was performed under thermodynamic conditions yielding predominantly the *cis* diastereomer. Although diastereoselectivity was not reported (as NMR did not exist at this time), van Tamelen introduced an equilibration step to enhance the diastereomeric ratio. After converting the cyclised acid to the corresponding ester, the mixture was treated with NaOEt to convert the kinetic diastereomer (*trans*) to the desired *cis* one. The presence of the *trans* diastereomer in this approach did not result in any complications, as the intramolecular nucleophilic substitution only occurs on the *cis* compound. For this transformation the equilibrated ester was reduced to the alcohol than converted to the corresponding bromide. Upon heating this compound in benzene, the pyridine nitrogen acted as a nucleophile, and the cyclisation resulted in a pyridinium salt. Oxidation of this pyridinium compound gave rise to the formation of the pyridone moiety, and *cytosine* was prepared upon debenzoylation. The

debenzylation was performed by using HI in the presence of auric chloride, but the role of the gold reagent is not discussed, van Tamelen cites an earlier reference for this procedure.¹⁸ This dealkylation approach is related to the well-known Hoffmann-elimination and called the Herzig-Meyer reaction which is used to quantitatively determine tertiary amines.¹⁹ Although the role of auric chloride is still not discussed, but it is suspected to be a catalyst for the reaction, as only a few drops of a dilute solution are used.

So far three enantioselective *cytisine* syntheses have been reported, two out of those yielding the unnatural enantiomer. Besides a formal synthesis, 9 racemic approaches have been reported. We will discuss here the approaches published after O'Brien's 2007 review.¹³ Gallagher published racemic synthesis which gives access to *cytisine* analogues.²⁰ Using a Stille coupling, the aromatic moiety of *cytisine* can be varied (Figure 61). The synthesis of the starting material for this approach was also published by him earlier along with a short racemic synthesis.²¹

Figure 61: Gallagher's modular *cytisine* synthesis

The latest reported *cytisine* synthesis by Cramer is based on a Ni catalysed annulation of pyridines (Figure 62).²²

Figure 62: Cramer's racemic cytisine synthesis.

The cyclisation precursor for this approach can be synthesised in two different ways and the asymmetric compound is available through enzymatic resolution prior to the linear sequence in Figure 63.²³

Figure 63: Synthesis of Cramer's starting material

The synthesis of the other natural products of interest was achieved by Honda.²⁴ His enantioselective synthesis yielded the unnatural enantiomers of *cytisine*, *jussiaeiine A*, *kuraramine*, and *isokuraramine*. To the best of our knowledge, his approach is the only reported one so far, where all four natural products are accessed through a late-stage common intermediate.

Figure 64: Honda's total synthesis

Honda's approach (Figure 64) starts from 4-hydroxyproline methyl ester and features a SmI_2 mediated ring expansion. This is followed by the introduction of the second chiral centre which proceeds without any diastereoselectivity, yielding a 1:1 mixture of the *cis* and *trans* 3,5-disubstituted piperidines. These isomers were inseparable, although upon reduction to the corresponding alcohols, chromatographic separation was carried out yielding *jussiaeiine A* and

its diastereomer. *Kuraramine* and *isokuraramine* were prepared via TMSI mediated *O*-demethylation.

Figure 65: Honda's cytosine synthesis.

Following the SmI_2 mediated key step in Figure 65, the piperidinone nitrogen was Bn protected and the second chiral centre was introduced as before, without diastereoselectivity. This mixture of esters was reduced to the corresponding alcohols and converted into mesylates. Upon heating, an intramolecular nucleophilic substitution occurs, similar to van Tamelen's approach yielding the bridged *cytosine* scaffold. The final product was obtained upon debenzylation.

For (+)-*kuraramine*, another enantioselective total synthesis was reported by Gallagher.²⁵ This bioinspired approach was based on the consideration that *kuraramine* might be a metabolite of *N*-methylcytosine.

Figure 66: Gallagher's bioinspired kuraramine synthesis

Cytisine was methylated then silylated, yielding a single diastereoisomer. Tamao-Fleming oxidation of the silylated intermediate followed by reduction gave *kuraramine*.

2.5 Follow up on the Prins reaction

In order to test the Prins chemistry on a suitable model system for the Lupin alkaloids, the corresponding β -substituted homoallylamine had to be synthesised. This would act as the precursor for the corresponding ene-sulfonamide using the hydroformylation reaction described in Chapter 1.4.

A convenient starting material for this model system was styrene oxide. Ring opening with vinylmagnesium chloride proceeded with complete regioselectivity giving access to β -phenyl homoallyl alcohol **2-1**. The hydroxyl group of this compound had to be converted to a tosylamide functionality (Figure 67).

Figure 67: Synthesis of β -substituted ene-sulfonamide

Alcohol **2-1** was activated initially via the corresponding mesylate which was intended to be converted into azide **2-2**. This would have given us amine **2-3** upon reduction. Unfortunately, the clean azide **2-2** was not obtained (according to IR spectrum) using standard conditions: sodium azide in DMF. Proceeding with the reduction of the azide mixture using acetic acid and zinc followed by treatment with tosyl chloride and base did not result in the formation of the desired tosylamide **2-5**, but the mesylate intermediate was recovered. It was concluded that the mesylate-azide conversion did not happen, and the IR spectrum of the crude product at that stage showed azide bands due to remaining sodium azide.

In order to obtain the desired product, a more powerful azide source, tetrabutylammonium azide was used.²⁶ Using this reagent azide **2-2** was obtained, and the reduction-tosylation sequence was attempted, but no tosylamide **2-5** was obtained. The intermediates were probably unstable during the reduction step. Azides are often unstable compounds, and in this case side reactions could be suspected as well: the vinyl group can be reduced as well as the azide; and the possibility of a cycloaddition can not be excluded.

Another pathway had to be found to synthesise the target compound: a strategy pioneered by Weinreb utilizes an amide Mitsunobu reaction for the alcohol-tosylamide conversion.²⁷

The carbamate partner for the Mitsunobu reaction was prepared by reacting tosyl isocyanate with methanol²⁸ and the reaction proceeded smoothly giving access to *N*-methyl tosylcarbamate **2-6** in excellent yield. The Mitsunobu reaction proceeded smoothly and the desired compound **2-5** was obtained upon removal of the *N*-methoxycarbonyl group using basic methanol.

The obtained homoallylamine **2-5** was converted to the corresponding ene-sulfonamide **2-7** via hydroformylation-intramolecular condensation reaction using the reaction conditions described in Chapter 1.4. This substrate reacted more slowly than the α -substituted one (Chapter 1.4), and the catalyst (Rh-BIPHEPHOS) amount was increased to 0.6 mol% which was proven to be sufficient.

Figure 68 Prins reaction of β -substituted ene-sulfonamides

When subjecting our ene-sulfonamide **2-7** to the Prins conditions a dimer product **2-9** was observed again, but in this case the desired Prins product **2-8** was formed as well. The mechanism for the dimer formation is analogous to the one discussed in Chapter 1.7. The ratio of the dimer and the Prins products was highly affected by the excess of the reagents and the solvent as well. Lower concentrations of available free formaldehyde favour dimer formation. When comparing solvents, DCM gave the best results. The Prins product was obtained in these cases was an 85:15 mixture of diastereomers. The slight loss of diastereoselectivity can be explained by the equatorial position of the phenyl substituent which has a weaker steric directing effect than the axial substituent in Chapter 1.7. The identity of the diastereomers was not investigated here.

Table 5: Prins reaction conditions using paraformaldehyde (% according to crude ^1H NMR)

LA (eq)	(CH ₂ O) _n eq.	T / °C	solvent	2-7 (%)	2-9 (%)	2-8 (%)
ZnCl ₂ (7)	12	25	DCM	22	28	50
ZnCl ₂ (7)	10	25	PhMe	13	55	32
ZnCl ₂ (4)	12	40	PhMe	0	57	43
ZnCl ₂ (2)	6	25	PhMe	25	57	18
ZnCl ₂ (3)	3	40	PhMe	7	67	26
ZnCl ₂ (2)	6	0	PhMe	100	0	0
ZnCl ₂ (1.4)	2.4	40	PhMe	6	64	30
ZnI ₂ (2)	3	35	Et ₂ O	0	69	31

Another formaldehyde source was tested: 1,3,5-trioxane, the cyclic trimer of formaldehyde. This change unfortunately did not yield any products. The starting material only disappeared when the mixture was heated to 110°C, but no product was obtained. It seems like trioxane was too stable – as a 6-membered ring – to break down to formaldehyde monomers under these conditions.

These compounds were not isolated, as the crude ^1H NMR spectra were sufficiently clean and the starting material to product ratios were easy to determine. Although these compounds were not reported before, their significant peaks in the spectrum are very similar to those in Chapter 1.7.

Table 6: Prins conditions using trioxane (% according to crude ¹H NMR)

LA (eq)	"CH ₂ O" eq	T / °C	solvent	2-7 (%)	2-9 (%)	2-8 (%)
ZnCl ₂ (7)	10	25	DCM	100	0	0
ZnCl ₂ (7)	12	40	PhMe	100	0	0
ZnCl ₂ (4)	12	110	PhMe	-	-	-
ZnI ₂ (2)	3	35	Et ₂ O	100	0	0

After discovering that trioxane is not efficient for the current reaction, varying the Lewis acid was the next logical step. Several experiments were performed but no product formation was observed. In the case of boron trifluoride diethyl etherate and ZnCl₂•TMEDA complex, starting material was recovered. Using stronger Lewis acids – regardless of reaction temperature and time – no products were obtained upon the consumption of the starting material. This indicated that too strong Lewis acids induce decomposition.

Table 7: Miscellaneous Prins reaction conditions (% according to crude ¹H NMR)

Lewis acid ^a	"CH ₂ O" ^b	T / °C	solvent	2-7 (%)	2-9 (%)	2-8 (%)
$\text{BF}_3 \cdot \text{OEt}_2$	trioxane	25	DCM	100	0	0
$\text{ZnCl}_2 \cdot \text{TMEDA}$	$(\text{CH}_2\text{O})_n$	40	PhMe	100	0	0
$\text{In}(\text{OTf})_3$	$(\text{CH}_2\text{O})_n$	40	PhMe	-	-	-
$\text{Ti}(\text{OiPr})_4$	$(\text{CH}_2\text{O})_n$	40	PhMe	100	0	0
$\text{Sc}(\text{OTf})_3$	$(\text{CH}_2\text{O})_n$	40	PhMe	-	-	-
SnI_2	$(\text{CH}_2\text{O})_n$	40	PhMe	43	50	7
FeBr_3	$(\text{CH}_2\text{O})_n$	40	PhMe	-	-	-
TMSOTf	$(\text{CH}_2\text{O})_n$	40	PhMe	-	-	-
$\text{Sc}(\text{OTf})_3$	$(\text{CH}_2\text{O})_n$	25	DCM	-	-	-
SnI_2	$(\text{CH}_2\text{O})_n$	25	DCM	88	12	0
FeBr_3	$(\text{CH}_2\text{O})_n$	25	DCM	-	-	-
TMSOTf	$(\text{CH}_2\text{O})_n$	25	DCM	-	-	-
MgBr_2	$(\text{CH}_2\text{O})_n$	35	Et_2O	-	-	-
$\text{Bi}(\text{OTf})_3$	$(\text{CH}_2\text{O})_n$	80	MeCN	-	-	-

^a: 1.2 eq Lewis acid used except $\text{BF}_3 \cdot \text{OEt}_2$ (5); ^b 2.4 eq. formaldehyde used except with $\text{BF}_3 \cdot \text{OEt}_2$ (10)

Unfortunately, the approach of performing the Prins reaction with simple reagents only showed limited success. As an alternative, synthetic equivalents to the formaldehyde monomer were used. For example (chloromethoxy)trimethylsilane²⁹ **2-10** was generated and used it in a one-pot procedure with ZnCl_2 but not desired Prins product **2-8** was obtained. According to the ¹H NMR spectrum of the crude material, the starting material decomposed.

Figure 69: Synthesis of a formaldehyde substitute reagent

Another approach to generate monomeric formaldehyde complexes was achieved through aluminium reagents. Reported procedures used trimethylaluminium³⁰ or trimethylaluminium combined with 2,6-diphenyl phenol³¹ which were described as reagents able to trap formaldehyde monomers as stable complexes. Using AlMe₃ and trioxane, the formation of the desired product **2-8** was not observed and starting material **2-7** was recovered.

As the last approach in this set of experiments formaldehyde gas was used as the ultimate monomer to obtain our Prins product **2-8** using the setup depicted in Figure 70.

Figure 70: Experimental setup for Prins reaction with formaldehyde gas

Paraformaldehyde was heated to 160 °C under a stream of nitrogen (to avoid building up large amount of formaldehyde gas in the heated flask, and to eliminate the chance of suck-back) and the resulting N₂/CH₂O mixture was transferred to the reaction flask through a Teflon tube and bubbled through a mixture of DCM/ZnCl₂/ene-sulfonamide **2-7**. The excess gas was passed through a set of bubblers. At first 20 equivalents of paraformaldehyde was used, which was passed through the reaction mixture cooled to 0 °C. Full conversion was not obtained (14% SM

in crude NMR), but the Prins product **2-8** was formed (22% in crude NMR). Unfortunately, the main product was the dimer **2-9** in this case as well (64% in crude NMR).

The reaction conditions needed to be changed. Low conversion and selectivity was probably caused by the short residence time or instability of formaldehyde in the reaction flask, and the temperature was lowered to -78 °C. In this case no dimer **2-9** formation was observed, the only product obtained was the Prins compound **2-8**. Unfortunately, the conversion was only 15% and the product was formed as a 1:1 mixture of diastereomers.

In order to find out the cause of failure in this system, formaldehyde was substituted by an actual monomeric aldehyde to see if the problem was the instability. The reaction was performed using acetaldehyde under the usual conditions ($\text{ZnCl}_2/\text{PhMe}/25^\circ\text{C}$) and a mixture of diastereomeric Prins products **2-11** was obtained (Figure 71). In total 4 diastereomers were formed as two sets of compounds. The ratio of the two main diastereomers was 3:1 and the ratios of the individual major:minor diastereomer pairs were 92:8 and 93:7. This shows some kind of diastereoselectivity since 4 new chiral centres were created and 2 major diastereomers were obtained. Most importantly this experiment has proved that our conditions for the Prins reaction are usable, but it is troublesome with formaldehyde.

Figure 71: Prins reaction using acetaldehyde

Despite the limited success on optimising this transformation, the total synthesis of Lupin alkaloids was still attempted. With a backup plan in hand, the synthesis of the β -pyridyl N-tosyl homoallylamine **2-15** key intermediate was attempted.

Figure 72: Retrosynthesis of the Prins strategy

The cyclic ene-sulfonamide substrate **2-14** for the Prins reaction could be obtained through the hydroformylation strategy used in Chapter 1.4. Upon a successful Prins reaction, the hemiaminal ether **2-13** could be subjected to hydrolysis and Lewis acid mediated *O*-dealkylation to yield the hydroxymethylpiperidine compound **2-12**.

Figure 73: Backup strategy for the hydroxymethylpiperidine synthesis

Alternatively, the cyclic ene-sulfonamide **2-14** can be iodinated followed by carbonylation. Hydrogenation of the C-C double bond of **2-17** should proceed with some diastereoselectivity and subsequent ester reduction would result in the desired hydroxymethyl intermediate **2-12**.

2.6 Attempted Total Synthesis of Lupin Alkaloids

The total synthesis of the target natural products was preceded by several unsuccessful cyclisation strategies. In some cases, the synthesis of the cyclisation precursor failed, while some cyclisation precursors gave a different ring closure than expected. These approaches provided compounds with interesting structural features and some exciting mechanistic insight into pyridine chemistry.

2.6.1 Total Synthesis of Lupin Alkaloids: Epoxide Ring Opening

As the model substrate described before was synthesised through epoxide ring opening, it seemed convenient to follow a similar strategy for the β -pyridyl compound **2-21** as well (Figure

74). Two routes were explored simultaneously: ring opening of 2-oxiranylpuridine **2-19** with vinylmagnesium halides and the ring opening of butadiene monoxide with metalopyridines **2-20**. At this point possible reaction pathways were still being investigated, so monosubstituted pyridines as model substrates were used. As butadiene monoxide is easily available in its enantiopure form using the Jacobsen HKR, compared to the pyridine epoxide, which has to be subjected to enzymatic resolution, the primary focus was on the butadiene monoxide strategy.

Figure 74: Epoxide ring opening strategies for a pyridine model system

2,6-Dibromopyridine was used as the starting material for this approach, and it was converted into 2-bromo-6-methoxypyridine **2-22** according to a simple literature procedure.³² The resulting 2-bromo-6-methoxypyridine was used as the test substrate for the epoxide ring opening reaction. A thorough study was performed varying bases, solvents, concentration, Lewis acid additives and the electrophile itself.

Figure 75: Epoxide ring opening strategy

The nucleophilic ring opening of butadiene monoxide is more challenging than other epoxides due to butadiene monoxide being an ambident electrophile. This compound can undergo ring opening at three different positions, which results in an increased number of possible side- and competing reactions.

Figure 76: Possible ring opening sites of butadiene monoxide

For our approach, selective ring opening on C2 is required. Besides this, nucleophiles can attack on C1 as well, and butadiene monoxide can undergo nucleophilic addition as well on C4.

Figure 77: Proposed ring opening of butadiene monoxide

As an initial approach, 2-bromo-6-methoxypyridine **2-22** was lithiated using *n*-BuLi and reacted with butadiene monoxide at low temperatures, as well as while warming up to room temperature (Figure 77). The ^1H NMR spectrum of the crude material of these reactions did not show the presence of the desired product. Starting material and 2-methoxypyridine was isolated. These results indicate that metalation did not go to completion, and moreover, the lithiopyridine did not react with the epoxide, but was quenched during the workup. Increasing the excess of *n*-BuLi yielded higher conversion in the metalation step, but starting material was still recovered. Complete metalation was only observed when the concentration of the reaction mixture was increased from 0.3 M to 1.5 M. Once evidence of complete metalation was observed, the role of the electrophile was investigated. When the lithiopyridine compound was reacted with DMF or iodine, the corresponding methoxypyridine carbaldehyde and 2-iodo-6-methoxypyridine were isolated in quantitative yield. It was concluded that under these conditions butadiene monoxide did not undergo the desired transformation. Due to the volatility of butadiene monoxide, it was never recovered. Also, no alkene peaks were present in the ^1H

NMR spectrum of the crude material, indication that butadiene monoxide did not undergo any reaction.

Butadiene monoxide was attempted to be activated by the addition of Lewis acids. Adding $\text{BF}_3 \cdot \text{OEt}_2$ to butadiene monoxide prior to the reaction with the nucleophile resulted in a complex mixture of compounds according to the ^1H NMR spectrum of the crude material, with the presence of several sets of terminal alkene protons. Unfortunately, no desired product was isolated.

When adding a solution of MgBr_2 to the lithiated pyridine before reacting it with butadiene monoxide, a 1:1 mixture of products (along with several other compounds) was observed in the crude NMR with terminal alkenes present. The identity of these products was not determined but it has shown that pyridyl Grignard reagents seem to be more effective for this transformation.

It has been reported that butadiene monoxide undergoes nucleophilic ring opening at C2 with 92-94% selectivity when reacted with 2-3 eq. of vinylmagnesium bromide.³³ Based on these considerations focus was shifted to Grignard reagents for the ring opening reactions. Unfortunately, the preparation of the 2-pyridyl Grignard reagents was not easy.

The Grignard reagent was prepared using 2-bromo-6-methoxypyridine and alkylmagnesium halides via halogen-magnesium exchange reaction³⁴ followed by the addition of butadiene monoxide for ring opening. Regardless of the Grignard reagent used ($i\text{PrMgCl}$, PhMgBr , EtMgCl), the halopyridine starting material was always recovered, indicating that metalation did not occur, as no H^+ quenched product (2-methoxypyridine) was observed. Increasing the concentration, temperature or the number of equivalents of the Grignard reagents did not result in any improvements. Changing the bromopyridine to the iodo compound resulted only in a slight increase in conversion (Figure 78).

Figure 78: Ring opening of butadiene monoxide with pyridyl Grignard reagents

Since the only experiment where any ring opening products were obtained was via the transmetalation of the lithiopyridine with MgBr_2 , it was suspected that the formed LiBr was of crucial significance. This theory was confirmed by the observations of Paul Knochel, who reported a significant increase in the Br/Mg exchange reaction of bromopyridines when LiCl was added to the reaction mixture.³⁵ He has commercialised this reagent as *TurboGrignard*, a THF solution of $^i\text{PrMgCl}$ and LiCl in equimolar ratio. Unfortunately, in our case, using homemade *TurboGrignard* was not successful, as no evidence of metalation was observed.

Another reported method for the formation of 2-pyridyl Grignard reagents is via using various lithium magnesiates.³⁶ A reagent of this type, $[\text{n-Bu}_2(^i\text{Pr})\text{Mg}]\text{Li}\cdot\text{LiCl}$ was prepared using $n\text{-BuLi}$ and $^i\text{PrMgCl}$ and reacted with 2-bromo-6-methoxypyridine, followed by the addition of butadiene monoxide. The main product of these reactions was 2-methoxypyridine, which indicated successful metalation, but the ring opening did not take place.

Zincate reagents have also been reported efficient in the metalation of bromopyridines.³⁷ One of these, $n\text{Bu}_4\text{ZnLi}_2\cdot\text{TMEDA}$ was prepared and used it as in the previous approaches, but no product was obtained in this reaction whatsoever.

The C-H functionalisation of pyridines at C6 was reported using directed metalation. The lithium salt of 2-dimethylaminoethanol³⁸ was shown to be efficient for this transformation, but in our case a complex mixture was obtained with no sign of the desired product.

Another approach to the direct C6 C-H functionalisation was reported by Paul Knochel.³⁹ The combination of $\text{BF}_3\cdot\text{OEt}_2$ and $\text{tmpMgCl}\cdot\text{LiCl}$ was shown to provide 75% yield when converting

2-methoxypyridine to 2-iodo-6-methoxypyridine. In our case, when using butadiene monoxide as the electrophile, a ring opening product was obtained which did not contain any pyridine moiety. This suggests the presence of a competing nucleophile. The identity of the product was not determined.

It had to be concluded, that butadiene monoxide, being an ambident electrophile is not suitable for this transformation, besides the difficulty in the metalation of halopyridines.

Work was continued with the backup plan of ring opening 2-oxiranyl-pyridine **2-19**. An easily accessible model system was used, and this epoxide was prepared using pyridine-2-carbaldehyde and trimethylsulfonium iodide in a Corey-Chaykovsky reaction (Figure 79).⁴⁰

Figure 79: Synthesis of 2-oxiranyl-pyridine

With the epoxide in hand, the ring opening was attempted using vinylmagnesium chloride. When performing the reaction at room temperature in either THF or Et₂O, an inseparable 1:1 mixture of products was obtained, which were possibly the ring opening products at C1 and C2 due to non regioselective nucleophilic attack. When the epoxide was activated with BF₃•OEt₂ at -78°C, followed by the addition of vinylmagnesium chloride, a single ring opening product **2-23** was obtained. Unfortunately, the ring opening was found to occur at the wrong position, and the epoxide was opened by the chloride ion instead of the vinyl anion (Figure 80).

Figure 80: Ring opening of 2-oxiranyl-pyridine

It had to be concluded that neither of our strategies yielded any of the desired products, thus the desired key intermediate **2-21** can not be obtained with this approach. Another alternative had to be found for the synthesis of the hydroformylation precursor compound.

2.6.2 Total Synthesis of Lupin Alkaloids: Tsuji-Trost Reaction

The synthesis of the hydroformylation precursor **2-25** was envisioned through a hydroamination using a tosylamide nucleophile to a 2-pyridyl substituted buta-1,3-diene **2-24**.

Figure 81: Proposed Michael addition to substituted butadiene

Vinylpyridines have been reported as Michael acceptor compounds before⁴¹ and their reactivity was intended to be exploited to access the β -substituted *N*-tosyl homoallylamine **2-25**.

As a first attempt, it was intended to synthesise a pyridyl-substituted butadiene through a Tsuji-Trost reaction, without the nucleophile component. An activated tertiary alcohol **2-26** was prepared, which upon elimination of the leaving group followed by deprotonation of the Tsuji-Trost π -allyl complex would have given us the butadiene intermediate **2-27**. It has been reported that these type of activated tertiary alcohols undergo elimination when treated with Pd(0) catalyst in the presence of base (Figure 82).⁴²

Figure 82: Proposed Tsuji-Trost reaction

The previously prepared 2-bromo-6-methoxypyridine³² **2-22** was used as a starting material for this synthetic approach. This bromopyridine was converted to the methyl ketone **2-27** upon

lithiation and reaction with *N*-acetyl Weinreb amide.⁴³ The obtained methyl ketone **2-27** was reacted with vinylmagnesium chloride to give the tertiary alcohol **2-28** (Figure 83).⁴²

Figure 83: Synthesis of the tertiary alcohol

At first alcohol **2-28** was reacted with SOCl_2 and pyridine to obtain the corresponding alkyl chloride. The conversion was successful, although a rearrangement was observed to the primary allylic chloride **2-29** (Figure 84). This rearrangement did not influence the outcome of our synthesis, as both the tertiary and primary allyl compound would give the same Pd-allyl complex.

Figure 84: Chlorination of the tertiary alcohol

The elimination reaction was attempted using base, but unfortunately the treatment of the obtained allylic chloride with KO^tBu did not yield the desired product, but a complex mixture of several unidentified products.

To avoid a nucleophilic attack during the Tsuji-Trost reaction, the alcohol **2-28** was activated as an acetate to have a weaker nucleophile leaving group. Using standard conditions (K_2CO_3 , Ac_2O , DMAP in DCM) no acetylated product was obtained. Resorting to harsher conditions,⁴⁴ *n*-BuLi and acetyl chloride was used. A conversion of 75% was obtained, but the isolated yield was only 17%, mostly due to the very similar R_f of the starting material and the product. It became clear, that the reaction had to be driven to completion in order to obtain the acetate

product in high yield. Unfortunately, elimination on this type of compounds occurs readily and the resulting dienes are highly reactive species, so the reaction conditions can not be too harsh.

Figure 85: Acylation of the tertiary alcohol

Table 8: Acetylation conditions

Base (eq)	Acylating agent (eq)	Additive (eq)	Solvent	T/°C	Conversion (%)*
K ₂ CO ₃ (1.2)	Ac ₂ O (1.2)	DMAP (0.1)	DCM	25 to 70	<5
<i>n</i> -BuLi (1.1)	AcCl (1.1)	-	Et ₂ O	25	75
<i>n</i> -BuLi (1.1)	Ac ₂ O (1.1)	-	Et ₂ O	25	50
<i>n</i> -BuLi (1.5)	AcCl (1.7)	-	Et ₂ O	25	60
<i>n</i> -BuLi (1.2)	Ac ₂ O (1.2)	-	Et ₂ O	25	33**
<i>n</i> -BuLi (1.1)	AcCl (1.1)	DMAP (0.1)	Et ₂ O	25	50
NaH (1.1)	AcCl (1.1)	-	THF	25	0
<i>n</i> -BuLi (1.2)	Ac ₂ O (5)	DMAP (0.1)	Et ₂ O	25	62

*: based on ¹H NMR; **: SM and Ac₂O premixed before the addition of *n*-BuLi

Unfortunately, full conversion was not achieved. Adding DMAP to the reaction mixture, or changing the acylating agent to the anhydride, or using excess reagents did not yield any improvement. The suspected cause of this is steric hindrance. It has to be noted that the acetate product was always obtained as a single regioisomer, the tertiary acetylated alcohol **2-30**.

Figure 86: Trifluoroacetylation of the tertiary alcohol

To overcome these difficulties, a more electrophilic reagent was used for the alcohol activation, trifluoroacetic anhydride. Upon reaction with *n*-Buli along with trifluoroacetic anhydride and DMAP, full conversion was obtained. The ^1H NMR spectrum of the crude material appeared to be a clean mixture of two compounds, the primary and tertiary trifluoroacetylated alcohol in 38:62 ratio, with a yield of 95%. When running the reaction at 0°C the isomer ratio was 9:1 (tertiary:primary) in yield of 92%. The products could not be separated using column chromatography, as the trifluoroacetate group underwent cleavage and the rearranged primary alcohol was obtained.

With the acetylated tertiary alcohol and the isomeric mixture of trifluoroacetylated alcohols in hand the Tsuji-Trost reaction was attempted. The activated alcohols were reacted initially in toluene with 10 mol% $\text{Pd}(\text{PPh}_3)_4$ at 25°C for 15 min, then the base was added.

Figure 87: Tsuji-Trost reaction of the acetylated tertiary alcohol

When the acetylated alcohol was reacted with $\text{Pd}(\text{PPh}_3)_4$ and DIPEA at room temperature, it rearranged to the linear acetylated alcohol, but no elimination was observed. When this mixture was heated to 110°C in toluene, a cyclodimer was formed via Diels-Alder reaction along with the rearranged product. When repeating this experiment at 110°C with DBU as the base, no rearranged product was present, only the cyclodimer along with one unidentified product which was inseparable from the cyclodimer. The formation of the cyclodimer can be explained by a [4+2] homo-Diels-Alder reaction which was been observed before in case of butadienes bearing an electron withdrawing group on the central carbon.⁴⁵

In order to determine if this approach can give access to the desired diene product, mechanistic studies were conducted using NMR spectroscopy. The trifluoroacetylated tertiary alcohol was

sonicated in a series of deuterated solvents with $\text{Pd}(\text{PPh}_3)_4$ for 5 min, then base was added. These reactions were sonicated at 25°C for several hours then heated to 50°C overnight. Regardless of the solvent (benzene- d_6 , chloroform- d , acetone- d_6 , THF- d_8) or the base used (Et_3N , TMG, DBU) only the rearrangement to the linear alcohol was obtained, along with the cleavage of the trifluoroacetyl group possibly due to the water present.

It had to be concluded that the desired 2-pyridyl-1,3-butadiene could not be prepared using this approach and the strategy had to be revised.

2.6.3 Total Synthesis of Lupin Alkaloids: Vinyl Iodide Coupling

The next approach for the butadiene synthesis was based on a proposed cross coupling of a pyridyl-substituted vinyl iodide with a metallo-vinyl reagent (Figure 88).

Figure 88: Proposed vinyl iodide coupling

The synthesis of vinyl iodides from hydrazones was pioneered by Sir Derek Barton.⁴⁶ Hydrazones react with iodine in the presence of a base to yield vinyl iodides. For this approach methoxypyridine-methyl ketone **2-27** used in the previous subchapter was converted to the corresponding hydrazone **2-36** using hydrazine monohydrate in methanol.⁴⁷ A screening of solvents, base and iodine sources was conducted using this compound **2-36** but unfortunately the desired vinyl iodide **2-35** was never obtained. In every case the azine dimer **2-37** was isolated which is the main byproduct of this transformation, as reported by Barton himself.

Barton systematically studied the key reaction parameters in order to minimise the azine formation.^{46b} He found that strong hindered bases such as guanidines increase the selectivity in favour of the vinyl iodide. As for the solvent, dry non-nucleophilic solvents, such as toluene,

ether or THF gave the best results. The biggest impact on the selectivity was shown by the order of addition. Originally the hydrazone and the base were mixed first, and the iodine was added later. In case of the more favourable inverse addition the hydrazone is added to a mixture of iodine and the base. Taking this study into consideration, different reaction conditions were attempted, but the desired vinyl iodide was not formed (Figure 89, Table 9).

Figure 89: The Barton reaction of hydrazides

Table 9: Summary of the Barton reaction conditions

base (eq)	I ⁺ source (eq)	solvent	T/°C	addition	product
Et ₃ N (3)	I ₂ (1.2)	THF	25	normal	2-37
TMG (4)	I ₂ (2.1)	THF	25	inverse	2-37
TMG (4)	ICl (2.1)	DCM	25	inverse	2-37:2-36 1:1
TMG (4)	I ₂ (2.1)	DCM	25	inverse	2-37
TMG (5.5)	I ₂ (2.1)	PhMe	25	inverse	2-37
TMG (12)	I ₂ (2.1)	PhMe	25	inverse	2-37
DBU (5.5)	I ₂ (2.1)	PhMe	25	inverse	2-37

According to the mechanism proposed by Barton^{46c} the hydrazone is oxidised by the iodine to yield the corresponding diazo compound. This can react with an iodonium ion to yield an iodo derivative which is converted into an iodocarbonium ion through loss of nitrogen. This key intermediate can either be deprotonated to yield the desired vinyl iodide, or react with the original hydrazone to give the azine byproduct (Figure 90).

Figure 90: Mechanism of the Barton reaction

It had to be concluded that using this approach, the desired vinyl iodide compound was not accessible. It seems like that the base was not strong enough and the reactive intermediates reacted with the hydrazone to yield the azine compound.

2.6.4 Total Synthesis of Lupin Alkaloids: Masked buta-1,3-diene

It has been reported that substituted sulfolenes undergo chelotropic elimination to yield buta-1,3-dienes substituted on the central carbon atoms.⁴⁸

Figure 91: Proposed sulfolene thermolysis

The coupling of sulfolenes with aryl iodides through a phosphine-free Heck reaction has been reported.⁴⁹ Following the original procedure with our substrate **2-47**, the desired product was formed, despite electron poor aryl compounds being reported to be unreactive (Figure 92).

Figure 92: Coupling of iodopyridine with sulfolene

2-Iodo-6-methoxypyridine **2-47** was obtained from 2-bromo-6-methoxypyridine **2-22** using lithiation as described before. Attempts to increase the yield for this reaction failed. Decreased temperature resulted in shutting down of the reaction, while increased temperature resulted in decomposition. Changing the catalyst to Pd(0) species such as Pd(PPh₃)₄ or Pd-dba complex did not result in product formation. Changing the solvent to acetonitrile surprisingly resulted in homocoupling of the iodopyridine giving 2,2'-dimethoxybipyridyl. The bromopyridine was also used for this reaction with Pd-dba catalyst and at higher temperatures, but only the bipyridyl byproduct was obtained along with the cyclodimer **2-34** discussed before.

The thermolysis of the coupled key intermediate **2-48** was attempted. The compound was heated in refluxing toluene overnight, but the reaction did not go to completion. The disappearance of the starting material was only observed after 48 h of reflux, and the cyclodimer product **2-34** was isolated (Figure 93).

Figure 93: Thermolysis yielding cyclodimer

The formation of cyclodimer **2-34** can be explained by a [4+2] cycloaddition of **2-26** as seen previously. At this point it had to be concluded that the desired key intermediate diene **2-26** was too reactive, and as such, it was impossible to isolate.

2.6.5 Total Synthesis of Lupin Alkaloids: 6-endo-dig Cyclisation

Another approach for the synthesis of the hydroformylation precursor **2-50** was proposed using a 6-endo-dig cyclisation. This methodology was reported by McDonald for the synthesis of dihydrofurans and dihydropyrans⁵⁰ initially and he extended this approach to *N*-heterocycles as well⁵¹. McDonald achieved these transformations using Mo and W carbonyl complexes under

irradiation. He proposed that these reactions involve the formation of vinylidene complexes, therefore they proceed with formal *endo*-selectivity (Figure 94).

As an alternative to McDonald's stoichiometric chemistry, catalytic silver⁵² and gold⁵³ reagents can also be used to activate alkynes.

Figure 94: Proposed 6-*endo*-dig cyclisation

In order to perform the cyclisation reactions, the cyclisation precursor β -substituted *N*-tosyl homopropargylamine had to be prepared, as a model system. Picoline was converted into pyridylacetic acid ethyl ester **2-51** using LDA and diethyl carbonate⁵⁴, which was alkylated⁵⁵ using LiHMDS and propargyl bromide followed by LiAlH₄ reduction to the corresponding alcohol **2-53**.⁵⁶ The hydroxyl group was converted into the tosylamide functionality using an amide Mitsunobu reaction with *N*-methyl tosylcarbamate followed by deprotection (Figure 95).²⁸

Figure 95: Synthesis of the cyclisation precursor

With the cyclisation precursor, the 6-*endo*-dig cyclisation was attempted. When AgOAc in DCE was used only decomposition of the starting material was observed. When the catalyst was changed to HAuCl₄•3H₂O under the same conditions, two products were isolated, but

unfortunately neither of them was the desired one. A methyl ketone **2-55** was obtained, resulting from the hydration of the alkyne along with an interesting indolizine product **2-56**. The formation of this can be explained by the pyridine nitrogen acting as the nucleophile in a 5-*exo-dig* cyclisation. The mechanism of the indolizine formation will be discussed later, along with another method yielding the same product. Yields are not representative for these reactions, as they were carried out on a very small scale (< 0.15 mmol) and the products were obtained in a few mg quantities, just enough for ^1H NMR characterisation.

Figure 96 Gold-catalysed cyclisation attempt

After the initial cyclisation approaches using simple silver and gold catalysts failed, the McDonald approach was attempted which has inspired us in the current synthesis strategy. McDonald has used a stoichiometric amount of $\text{Mo}(\text{CO})_5\text{L}$ or $\text{W}(\text{CO})_5\text{L}$ where L was a labile ligand, such as THF. These complexes were generated under irradiation, but we did not have access to photochemical reactors, so they had to be prepared under non-irradiative conditions. It has been reported that $\text{M}(\text{CO})_6$ complexes can be converted to $\text{M}(\text{CO})_5(\text{NMe}_3)$ species⁵⁷ using anhydrous trimethylamine *N*-oxide (TMANO)⁵⁸ through oxidation of one CO ligand to CO_2 .

The metal reagent was prepared by stirring the metal hexacarbonyl (Mo, W) with Me_3NO in THF for 1 day then alkyne **2-54** and triethylamine was added. Upon stirring for 2 days at room temperature, no identifiable product was isolated. Repeating the cyclisation step at reflux temperature yielded no identifiable product in case of tungsten, but when molybdenum was used, the previously shown indolizine product was isolated (Figure 97).

Figure 97: Molybdenum-mediated cyclisation

With McDonald's method, which reportedly proceeds through a vinylidene complex, it was rather odd that an indolizine product was obtained, which indicates an *exo* cyclisation. This is not consistent with the vinylidene complex intermediate and the following mechanism is proposed (Figure 98).

Figure 98: Proposed mechanisms for Au and Mo mediated indolizine formation

As it is proposed, the vinylidene complex **2-57** is not being formed because the molybdenum is chelated between the alkyne and the pyridine nitrogen **2-58**. This coordination complex allows migratory insertion of the alkyne into the nitrogen-molybdenum bond, forming the

indolizine scaffold **2-59**. Aromaticity is restored via deprotonation and protolysis of the carbon-molybdenum bond followed by a double bond isomerisation.

In case of the gold catalysed approach, the alkyne is activated by the gold catalyst followed by attack of the pyridine nitrogen **2-61** which is a stronger nucleophile than the sulphonamide. Deprotonation, possibly by the eliminated chloride anion and protolysis of the gold species yields the same final intermediate **2-60** as the molybdenum approach and the indolizine product **2-56** is formed via double bond isomerisation which is driven by the formation of an aromatic ring.

A similar approach was reported by Gevorgyan for the synthesis of indolizines using similar substrates, but different catalysts.⁵⁹ Another example of a similar reaction is a base mediated reaction yielding the indolizine, although this is unpublished.⁶⁰ The indolizine **2-64** is obtained alongside the two regioisomeric OMe addition products (Figure 99).

Figure 99: Indolizine synthesis by Boonsombat

At this point it had to be concluded that the pyridine nitrogen is more nucleophilic than the sulphonamide, thus the cyclisation was not feasible on this model system. Our target natural products feature a 2,6-disubstituted pyridine moiety with a methoxy group in position 6, so it seemed logical to prepare the 6-methoxy group containing cyclisation precursor **2-67** which would be significantly less nucleophilic due to steric shielding of the pyridine nitrogen. The synthesis of the model substrate was repeated using 6-methoxy-2-methylpyridine⁶¹ as the starting material. For our surprise the functionalisation of the methyl group with diethyl carbonate only proceeded with 16% yield and no further increase was obtained upon

optimisation. Regardless of this, the 6-methoxy containing cyclisation precursor **2-67** was prepared, along with the 6-bromo containing analogue **2-68** (starting from 2-bromo-6-methylpyridine, Figure 100) using the same route as in the case of **2-54** (Figure 95).

Figure 100: Synthesis of further cyclisation precursors

The obtained amount of the methoxy compound **2-67** was not enough for the cyclisation, the bromo substrate **2-68** was used as the model substrate from here on, which is even less nucleophilic than the methoxy compound. No indolizine product **2-56** was obtained in this case, but the methyl ketone **2-55** was formed when using $\text{HAuCl}_4 \cdot \text{H}_2\text{O}$, $\text{W}(\text{CO})_5(\text{NMe}_3)$, or AgOTf . No identifiable product was isolated when we used $\text{Mo}(\text{CO})_5(\text{NMe}_3)$ or PPh_3AuCl with AgOTf . When using AgOAc in refluxing DCE the formation of the desired 6-endo-dig product **2-70** was observed. Unfortunately, this was the minor compound besides the 5-exo-dig cyclisation product **2-69** (Figure 101).

Figure 101: AgOAc mediated cyclisation

The cyclisation products were identified using ^1H NMR spectroscopy. In the case of the 5-membered major compound **2-69** the presence of a peak at 2.17 ppm integrating to 3 and showing long-range coupling indicated the presence of an isolated methyl group connected to

an olefin. Furthermore, the 5.01 ppm peak of the olefinic proton showed reduced multiplicity compared to the other product, indicating the proposed 5-membered ring structure (Figure 102).

Figure 102: NMR spectrum of the 5-exo-dig product **2-69**

The 6-endo-dig product **2-70** was identified by the presence of the characteristic doublet of the cyclic ene-sulfonamides at 6.7 ppm belonging to the olefinic proton α to the nitrogen. Furthermore, the high multiplicity of the 5.10 ppm peak of the other olefinic proton also indicated the 6-membered ring structure (Figure 103).

Figure 103: NMR spectrum of the 6-endo-dig product 2-70

Both the 5-*exo-dig* and 6-*endo-dig* cyclisation are favoured according to Baldwin's rules.⁶² It had to be concluded that this approach is too troublesome to apply in total synthesis. The reaction is extremely sensitive to water (alkyne hydration product), and it seems like that the formation of the 5-*exo-dig* cyclisation product is the dominating pathway under these conditions.

2.7 Total Synthesis of Lupin alkaloids: 6-*endo* aza-Michael cyclisation

Our group has used intramolecular Michael additions extensively for the total synthesis of natural products. 6-*exo* oxa-Michael addition was used in the syntheses of Diospongins A,⁶³ Cyanolide A,⁶⁴ Curvulone B,⁶⁵ and the THP rings of Clavosolide A⁶⁶ and Bistramide D.⁶⁷

According to Baldwin's rules⁶² both the 6-*endo-trig* and 6-*exo-trig* cyclisation are favoured. On top of this, a competing 5-*exo-trig* pathway is favoured, making this transformation challenging and versatile at the same time.

Examples of 6-*endo* oxa-Michael reactions used in total synthesis can be found in the literature, such as Rizzacasa's synthesis of *Apicularen A* (Figure 104).⁶⁸

Figure 104: 6-*endo* oxa-Michael reaction in the total synthesis of *Apicularen A*

The success of these approaches encouraged us to extend this methodology to nitrogen heterocycles, and attempt the total synthesis of piperidine alkaloids, such as the Lupin family using a 6-*endo* aza-Michael reaction.

2.7.1 Aza-Michael Cyclisation in Total Synthesis

Only found a handful of examples were found in the literature reporting *endo aza*-Michael reactions. One of these is Kim's formal synthesis of *Lasubine II*.⁶⁹ In this approach a sequential reduction-cyclisation cascade is present, involving an *in situ 6-endo-dig aza*-Michael reaction upon Cbz deprotection. The cyclisation was achieved upon heating the mixture at reflux in MeOH for 2 days, and the yield was 37%. As there was no base added to the reaction, the low yield can be explained by the hydroxypiperidine nitrogen being present as its hydrochloride salt, unable to participate in the S_N2 ring closure (Figure 105).

Figure 105: *endo aza*-Michael cyclisation involved in the synthesis of *Lasubine II*

A *6-endo-trig aza*-Michael reaction is reported in Pandey's synthesis of *epi-7-deoxypancratistatins*.⁷⁰ In this case, harsher conditions are required, as the Michael donor is a Cbz protected nitrogen. Due to the weak nucleophilicity of this functionality, it had to be deprotonated using *n*-BuLi to form the more reactive anion. The cyclisation product **2-77** was obtained as a single diastereoisomer due to steric control arising from the highly substituted cyclohexenone ring (Figure 106).

Figure 106: Pandey's *aza*-Michael reaction

Tokuyama has demonstrated another *6-endo-trig* *aza*-Michael reaction during his total synthesis of *Petrosin*.⁷¹ The quinolizidine moiety of the natural product was constructed using the *aza*-Michael strategy. Interestingly both basic and mildly acidic conditions deliver the same product **2-79** as a single diastereoisomer, with the same yield. However, the cyclisation was complete in 20 minutes when using wet silica in chloroform, while ammonia in methanol took 12 hours. It appears that the acidic activation of the Michael acceptor is more efficient in this case (Figure 107).

Figure 107: Tokuyama's *aza*-Michael strategy for quinolizidine synthesis

The first example of an *endo aza*-Michael reaction where due to the lack of strong steric control two diastereoisomers are being formed is reported in Hou's synthesis of *Lentiginosine*.⁷² This is in fact a double *aza*-Michael reaction, one intermolecular followed by one intramolecular addition. The main product here is both thermodynamically and kinetically favoured, according to theoretical calculations and epimerisation experiments. The modest stereoselectivity in this case was expected as the existing stereocentres are outside the formed ring (Figure 108).

Figure 108: Hou's *aza*-Michael strategy yielding diastereomers

Fustero has reported a base mediated intramolecular *6-endo-trig* *aza*-Michael reaction during his synthesis of *Myrtine* along with an organocatalytic *6-exo-trig* *aza*-Michael reaction.⁷³ The

base catalysed cyclisation yielded *Mytrine* as a single diastereomer, due to the strong stereochemical control of the chiral centre α to the nitrogen. In contrast to the previous example, the existing stereocentre is inside the formed ring, which means it is able to influence the 6-membered transition state (Figure 109).

Figure 109: Aza-Michael reactions reported by Fustero

Another piperidine synthesis involving a 6-endo-trig *aza*-Michael reaction is reported by Georgiadis.⁷⁴ Unfortunately the stereoselectivity of this reaction is not discussed, the product is described as ‘4 pairs of enantiomers’ which is assumed to mean stereoisomers. However, interestingly it is mentioned that the use of a caesium base is crucial. They have observed a competitive 6-*exo*-trig cyclisation with the ethoxycarbonyl group, yielding a lactam product when they used DBU or acid catalysis. However, they don’t mention trying other carbonate bases, so the crucial part might be the carbonate, not necessarily the caesium (Figure 110).

Figure 110: *aza*-Michael cyclisation reported by Georgiadis

A double *aza*-Michael cyclisation is used in Molander’s total synthesis of *Cylindricine C*.⁷⁵ Besides the discussed 6-*endo*-trig reaction, a 5-*exo*-trig is taking place in a sequential fashion (Figure 111).

Figure 111: Double aza-Michael cyclisation towards Cylindricine C

Further examples can be found in the literature for *endo* aza-Michael cyclisation yielding pyrrolidines. However, in this case the 5-*endo-trig* cyclisation is disfavoured by Baldwin⁶² and is often competing with the 5-*exo-trig* pathway typically yielding lactams instead of the saturated heterocycles.

In the work of Thebtaranonth a systematic study can be found on the factors influencing the *endo/exo* selectivity, which we will not discuss here (Figure 112).

Figure 112: Thebtaranonth's double aza-Michael reactions

This problem was eliminated by Iwai, about 20 years later.⁷⁶ He has shown that the formation of the lactam product through a 5-*exo-trig* reaction proceeds via reversible steps, and the appropriate choice of the Michael acceptor as well as the Michael donor (with emphasis on the *N*-protecting group) can promote the disfavoured 5-*endo-trig* pathway. In his study sulphonamidate nucleophiles were proven to be successful in combination with alkyl esters, due to them being better leaving groups. Another improvement was the replacement of esters to trihalomethyl groups. Particularly CF₃ and CCl₃ functionalities afforded the highest selectivity for the *endo* cyclisation. Although the reactions of these trihalomethyl compounds proceed through an S_N2' mechanism, it is a valuable alternative to Michael additions (Figure 113).

Figure 113: Iwai's endo-selective cyclisation

Double *aza*-Michael reactions are extensively used for the synthesis of piperidinones. As these types of compounds are not of our interest, just one example will be shown without further discussion (Figure 114).⁷⁷

Figure 114: Rosiak's double *aza*-Michael reaction yielding piperidinone

2.7.2 Total Synthesis of rac-Cytisine

In order to construct the piperidine ring of the target alkaloids, the linear cyclisation precursor had to be designed first. Since the target alkaloids bear a pyridone or a methoxypyridine ring in position 3 and a hydroxymethyl group in position 5, surrogates of these functionalities have to be present in the cyclisation precursor (Figure 115).

Figure 115: Proposed 6-endo-trig *aza*-Michael cyclisation

The Michael donor was chosen to be a sulphonamide nucleophile, as our laboratory has extensive experience in the chemistry of these compounds. The Michael acceptor was proposed

to be a vinylic ester, and the pyridine moiety could be either a pyridone, a methoxypyridine, or a halopyridine as these three functionalities are in principle interconvertible.

The proposed cyclisation strategy was based on the intention to effect stereocontrol via the conformation of the six-membered ring transition state by the existing stereocenter. Although the pyridyl substituent would occupy an equatorial position in the transition state, stereoselectivity was still expected from the system. It was also intended to explore cyclisation conditions in order to get access to both the *cis* and *trans* 3,5-disubstituted piperidines selectively, making this synthetic approach stereodivergent.

2.7.2.1 Synthesis of the Cyclisation Precursor

The structure of the cyclisation precursor is similar to the one discussed earlier in Chapter 2.6.5, and it can be prepared using a very similar route.

It was mentioned before that the functionalisation of the picoline methyl group proceeded with low conversion if a methoxy substituent was present and only delivered high yield when it was changed to a bromopicoline (Figure 98). Further experiments with other alkoxy substituents (OBn) on the pyridine, or 2-methylpyridones as well as *N*-protected (MOM, OBn) 2-methylpyridones did not result in the desired transformation.

Figure 116: Functionalisation of bromopicoline

In view of these results, 2-bromo-6-methylpyridine was used as starting material for the total synthesis. Modifying the procedure of O'Brien⁵⁴, which involved the reaction of picoline with 2.05 equivalents of LDA followed by the addition of 3 equivalents of diethyl carbonate at -78°C, the bromo analogue product **2-68** was obtained in quantitative yield. It was found that

the optimal reaction temperature is -40°C for the bromopicoline and the number of equivalents of diethyl carbonate can be reduced to 2. The order of addition was also modified for our convenience. A mixture of 2-bromopicoline and diethyl carbonate in THF was added to LDA in THF at -78°C and reacted at -40°C overnight. It was found during the optimisation stage (at small scales) that cannulating LDA results in some loss of the reagent, and this addition order was maintained during scale-up as well. The 2 equivalents of LDA are required for the reaction as the α -methylene group of the product is more acidic than the bromopicoline methyl group, just as in a classical Claisen condensation. The product is obtained in quantitative yield after standard aqueous workup and thorough drying *in vacuo* to remove excess diethyl carbonate.

As it was mentioned before the synthesis of this substrate would be analogous to the one discussed in case of the alkyne cyclisation precursor in Chapter 2.6.5. In that subchapter propargyl bromide was used to alkylate the bromopyridylacetic acid ethyl ester **2-68**, here a different alkylating agent had to be used. As the intermediate already contains one ester group which undergoes reduction in the next step, the alkylating moiety had to be a surrogate for the vinyl ester Michael acceptor functionality to avoid competitive reduction. After these considerations, a vinyl iodide moiety was chosen as the surrogate Michael acceptor as this can be converted to the ester using carbonylation. The alkylating agent **2-103** is a known compound, and can be prepared in 2 steps from propargyl alcohol.⁷⁸ Hydrogen iodide addition followed by bromination yields the alkylating agent in a low yield of 25-30% over 2 steps: the iodoalcohol intermediate **2-102** has to be extracted from a high volume of aqueous acetonitrile and the dihalogenated product **20-103** seems to partially decompose upon distillation (Figure 117).

The addition of HI proceeds with complete regioselectivity according to Markovnikov's rule, as two alkene singlets are present in the ^1H NMR spectrum of both **2-102** and **2-103**.

Figure 117: Kishi's procedure

With the alkylating agent in hand the alkylation was attempted using the conditions of Lee.⁵⁵ The ester **2-66** was deprotonated using LiHMDS at -78°C in THF and the alkylating agent **2-103** was added 15 minutes later. The mixture was allowed to warm up to room temperature overnight and the product **2-104** was obtained in 65% yield after aqueous workup and column chromatography. A small amount (5%) of over alkylated byproduct was obtained as well, and to eliminate this, the amount of the alkylating agent **2-104** was reduced to 0.95 equivalents which resulted in the yield increasing to 69% (Figure 118).

Figure 118: Alkylation using 3-bromo-2-iodopropene

From this point onward, all iodo containing intermediates were considered as light sensitive compounds. As precaution, all reaction flasks, columns and rotary evaporators were covered by aluminium foil. In addition, the fume hood lights were turned off and these compounds were stored in the refrigerator.

For the conversion of the ester moiety to the tosylamide **2-107** the same methodology was used as in the chapters before. The ester was reduced to the corresponding alcohol **2-105** which was subjected to an amide Mitsunobu reaction followed by deprotection as mentioned before.²⁸ The yields in this sequence were delightfully high, 85% for the reduction, 79% for the amide Mitsunobu reaction, and 91% for the deprotection step (Figure 119).

Figure 119: Introduction of the Michael donor functionality

With these three steps the Michael donor functionality was introduced. However, the product of the Mitsunobu reaction was difficult to purify via column chromatography as the byproduct diisopropyl hydrazinedicarboxylate was co-eluting. In order to eliminate this problem, di-*t*-butyl-azodicarboxylate (DTAD) was used in the Mitsunobu reaction.⁷⁹ This reagent is superior over the regularly used DEAD or DIAD, as both DTAD and its reduced form can be removed from the reaction mixture upon treatment with trifluoroacetic acid (Figure 120).

Figure 120: Acidic removal of Mitsunobu reagents

The last step towards the synthesis of the cyclisation precursor was the conversion of the vinyl iodide moiety to the ester. This was achieved using a simple carbonylation reaction with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in the presence of triethylamine, methanol and CO (1 atm) at room temperature. Under these extremely mild conditions the bromopyridine moiety is intact and the product is obtained in excellent yield. In general, carbonylation reactions of vinyl iodides are reported to require heating, but a few examples can be found where neither heat nor pressure is required.⁸⁰

The synthesis of the cyclisation precursor **2-108** was achieved in 6 linear steps with 33% overall yield (Figure 121).

Figure 121: Synthesis of the cyclisation precursor

2.7.2.2 Optimisation of the *aza*-Michael cyclisation

The *aza*-Michael cyclisation was attempted under different conditions involving a base, solvent and temperature screening. Different type of strong bases were tested for the cyclisation ranging from inorganic carbonate through tertiary amine to hydride to nucleophilic and non-nucleophilic organic bases. In each case two diastereomers were obtained. At that stage the identity of the diastereomers was unknown and they were differentiated by the ^1H NMR chemical shift of their methyl ester singlet until they were identified later. For the sake of discussion, the identity of these compounds will be revealed before their identification will be discussed.

A very clear trend was shown during this screening. The major product at lower temperatures was the *trans* diastereomer **2-109**, while at higher temperature the *cis* **2-110** was obtained mainly (Figure 122, Table 10).

Figure 122: aza-Michael cyclisation

Table 10: Optimisation of the aza-Michael cyclisation conditions

base	T/°C	solvent	conversion (%)	2-109 (%)	2-110s (%)	dr
Cs ₂ CO ₃	-5	THF	71	65	6	91:9
Cs ₂ CO ₃	0	THF	100	88	12	88:12
LiHMDS	0	THF	100	95	5	95:5
Cs ₂ CO ₃	25	THF	100	43	57	43:57
KO ^t Bu	25	THF	100	-	-	-
DIPEA	60	THF	0	-	-	-
NaH	60	THF	100	-	-	-
TMG	60	THF	83	38	45	46:54
DBU	60	THF	100	38	62	38:62
DBU	100	dioxane	100	27	73	27:73

1 eq base was used for all approaches and reactions were ran overnight unless TLC indicated the consumption of SM

In case of the reactions at lower temperatures Cs₂CO₃ was used according to *in-house* procedures for the deprotonation of sulphonamides. The obtained diastereoselectivity was always around 9:1 at 0°C and the *trans* compound **2-109** being the main product. However, the reaction was rather slow, often taking 1-3 days to go to completion. It was concluded that Cs₂CO₃ has a very low solubility in THF and even with pre-solubilising (sonicating Cs₂CO₃ in THF before adding the cyclisation precursor) full conversion was not always obtained. Later changing to a homogenous base, LiHMDS, this problem was eliminated. However, the reaction was still slow, it took 35 hours to go to completion. On the other hand, diastereoselectivity was improved to 95:5.

When the cyclisation was ran at room temperature (23°C) with Cs₂CO₃ a diastereoselectivity of 47:53 was obtained where the major product was the *cis* diastereomer **2-110** and the reaction

went to completion in a matter of hours. When changing the base to KO^tBu at room temperature an unidentified alkene product was indicated by ¹H NMR.

When the temperature was raised, the major product became the *cis* diastereomer **2-110**. When using DIPEA as the base, no conversion was obtained in THF at 60°C. In the case of NaH, no conversion was indicated by TLC at room temperature, and decarboxylation was observed at 60°C by ¹H NMR. When using TMG under the same conditions a *dr* of 46:54 was observed, while DBU provided a *dr* of 38:62. When changing the solvent to 1,4-dioxane and the temperature was raised to 100°C a *dr* of 27:73 was observed. Further increase in the temperature (sealed vial) resulted in decomposition. The optimal conditions were identified through this study and later used in the total syntheses of the target natural products.

2.7.2.3 Identifying the Individual Diastereoisomers

When discussing the stereochemical outcome of the reaction, kinetic and thermodynamic preferences have to be considered. In general, it is easier to predict which product would be the thermodynamically favoured. In order to do this, the *A values*⁸ of the substituents have to be compared.

Figure 123: Diastereomeric aza-Michael products

⁸ IUPAC defines the *A* value as “Winstein-Holness *A* value: The conformational preference of an equatorial compared to an axial substituent in a monosubstituted cyclohexane. This steric substituent parameter equals in $\Delta_r G^0$ in kcal•mol⁻¹ for the equatorial to axial equilibration on cyclohexane. The values are also known as 'Winstein-Holness' *A* values.” *Pure and Applied Chemistry* **1994**, 66, 1077.

The *A value* of a CO₂CH₃ group is 1.27 kcal/mol, while there is no available value for a pyridine ring, however the *A value* of a phenyl group is 3 kcal/mol which is a good approximation in this case. This means that the pyridyl group with the larger *A value* occupies an equatorial position in both diastereomers, while the methoxycarbonyl group will be equatorial in the *cis* and axial in the *trans* form. According to the *A values* the energy difference between the diastereomers is approximately 0.6 kcal/mol, as the *A value* arises from two 1,3-diaxial interactions on monosubstituted cyclohexanes while in these molecules, just one 1,3-diaxial interaction is present. These numbers indicate that the *cis* cyclised product is the thermodynamically favoured one (Figure 123).

Additional proof was obtained to support the *A-value* based theory from DFT calculations, done by Dániel Csókás, a fellow PhD student in our group. Structure optimisation was conducted on B3LYP/6-311G(d) base in vacuum and the energy difference was calculated to be 0.459 kcal/mol in favour of the *cis* diastereomer which is in alignment with the previous theory. This indicates that the *dr* obtained at 100°C in the presence of DBU corresponds to an equilibrium mixture, and further optimisation would not lead to better stereoselectivity (Figure 124).

Figure 124: DFT optimised structures 2-110 (left); 2-109 (right)

The diastereoselectivity can be explained. In case of the reaction at low temperature, which we postulate is controlled kinetically, the post-cyclisation protonation step determines the configuration. As it is depicted below, there is a steric clash on the top face of the ring due to

the 1,3-diaxial interaction with the C3 hydrogen, thus protonation of the enolate will proceed from the bottom face ultimately forcing the methoxycarbonyl group into the *axial* position, yielding the *trans* conformer (Figure 125).

At high temperatures, under thermodynamic control, the product ester can be deprotonated in the α position and equilibrate to the lower energy product. In case of the low temperature reaction, the deprotonation is either too slow or even can not occur, and the equilibrium can't be reached.

Figure

125: Origin of diastereoselectivity in the aza-Michael cyclisation under kinetic control

Already van Tamelen has described the equilibration during his synthesis of cytosine to enhance the diastereomeric ratio in favour of the *cis* 3,5-disubstituted piperidine product. Van Tamelen's synthesis was carried out around the same time as Zimmermann first reported his equilibration study on disubstituted cyclohexanes.⁸¹

Further proof was collected from experimental evidence. The diastereomeric mixture obtained at 100°C was reduced to the corresponding mixture of alcohols which were separated via column chromatography, showing the same *dr* as the esters before, indicating no epimerisation. One of these alcohol diastereomers was crystalline and it was subjected to single crystal X-ray diffraction. The crystal structure showed this compound to have a *cis* configuration. After the

crystal was inspected, it was retrieved from the X-ray facility and subjected to ^1H NMR. The proton spectrum indicated a diastereopure sample and the chemical shifts aligned with those of the major diastereomer. Once more, it was concluded that the cyclisation at high temperatures yields the *cis* diastereomer as the major one (Figure 126).

Figure 126: X-ray structure of the reduced *cis* alcohol **114** obtained from ester reduction

Further experimental proof will be discussed later along with the total synthesis of racemic *cytisine*.

2.7.2.4 Synthesis of Racemic Cytisine

As mentioned before, the cyclisation mixture was reduced to the corresponding alcohols which are separable chromatographically. In case of *cytisine* the alcohols were not separated, as the proposed synthesis strategy was similar to the one reported by van Tamelen involving an intramolecular cyclisation.^{14b} He reported that only the *cis* compound is able to cyclise, the *trans* remains intact.

In view of van Tamelen's results the diastereomeric mixture of alcohols **2-113/2-114** was converted to the corresponding mesylates **2-115/2-116** using MsCl and Et_3N in DCM which were obtained in quantitative yield. Upon heating the mesylates in chloroform to 60°C the *cis* mesylate **2-116** cyclised and the obtained bromopyridinium mesylate salt **2-117** was hydrolysed

to the pyridone by the addition of aq. Na_2CO_3 in a mild one-pot procedure. The obtained *N*-tosylcytisine **2-118** was easily separable via column chromatography from the unreacted *trans* mesylate **2-115** (Figure 127).

Figure 127: Synthesis of *N*-tosylcytisine

It has to be noted that heating is essential for the cyclisation to proceed as only the 3,5-diaxial conformation of the *cis* mesylate **2-116** can undergo the reaction. When such conformational issues are not limiting the transformation, intramolecular $\text{S}_{\text{N}}2$ reactions involving an alkyl mesylate and a pyridine nitrogen proceed instantaneously as it has been reported in the synthesis of *Tashiromine*.⁸²

With *N*-tosylcytisine **2-118** in hand, detosylation was attempted using magnesium and methanol under sonication. The ^1H NMR spectrum of the crude material of the reaction mixture showed the absence of tosyl peaks, which was delightful, but it also showed the absence of pyridone peaks. Repeating the reaction with proper temperature control delivered the same results. It was concluded that the pyridone moiety undergoes competitive reduction. Although the product was isolated, it was unidentified, and the obtained ^1H NMR data did not match the reported spectrum for tetrahydrocytisine (Figure 128).⁸³

Figure 128: Failed detosylation

Since the existing methods for the tosyl group removal are mostly reductive approaches it had to be evaluated if the tosyl group can be removed without the pyridone undergoing reduction. Comparison of the reduction potentials of the two moieties seemed like a good approach, but these values were not found in the literature.

In order to determine these values, the individual building blocks had to be prepared separately and measured via cyclic voltammetry (CV). *N*-tosylpiperidine⁸⁴ was synthesised by reacting piperidine with tosyl chloride in ethanol, while *N*-methylpyridone⁸⁵ was accessed through the *N*-methylation of pyridone with methyl iodide in the presence of sodium carbonate in acetone. These building blocks were investigated with CV against a ferrocene standard in the Webster laboratory by Gan Sher Li. It was found that the reduction potentials of these compounds does not differ significantly from each other. The difference turned out to be 3 mV, which meant that selective reduction was impossible, regardless of reagent. Interestingly, no reoxidation band was found in the cyclic voltammogram of *N*-methylpyridone, indicating a possible reductive and irreversible ring opening (Figure 129).

Despite the well-known difficulties of the tosyl group removal, our group has extensive experience in using this protecting group in total synthesis, especially in the ones utilising hydroformylation as the choice for piperidine synthesis. The choice of using the tosyl group was made based on experience, however, alternatives could have been considered earlier.

Figure 129: Cyclic voltammograms of *N*-tosylcytisine fragments

Once it was concluded that the tosyl group is not a suitable protecting group for the synthesis of *cytisine*, an alternative had to be found. The 2-nitrobenzenesulfonyl (nosyl) group seemed like an appropriate choice, as it can be removed through the reaction with nucleophiles and the byproducts are easily separable (Figure 130).⁸⁶

Figure 130: Removal of tosyl and nosyl groups

The synthesis was started over at this point using the exact same scheme, except for the Mitsunobu reaction where *N*-nosyl methylcarbamate⁸⁷ was used, which can be prepared in 2 easy steps from nosyl chloride **2-126** (Figure 131).

Figure 131: Synthesis of the nosyl carbamate reagent

Changing the tosyl group to nosyl did not influence any of the steps in the reaction scheme, except the Mitsunobu reaction. The decreased nucleophilicity of the nosyl carbamate results in an incomplete reaction, even when refluxing overnight. However, the alcohol starting material can be recovered, thus the yield remains the same as before, through the recovery of starting material. Also, the products of the *aza*-Michael reaction **2-132** become separable via column chromatography upon switching to the nosyl group, but the corresponding alcohols **2-133** were not.

Figure 132: Total synthesis of racemic cytosine

The removal of the nosyl group proceeded smoothly with potassium thiophenolate providing **2-119** in almost quantitative yield. With this, the total synthesis of racemic cytosine was completed in 11 linear steps with 16% overall yield.

This reported approach for the total synthesis of racemic cytosine involved the rational design of a cyclisation precursor possessing surrogate functionalities of what are present in the natural products. The strategy was proven to be stereodivergent which is the first reported one of its kind. As the following subchapters will discuss it, this methodology can be used for the total synthesis of further Lupin alkaloids and can be modified to be enantioselective.

2.7.3 Studies Towards Further Lupin Alkaloids

As it was proposed, additional natural products were intended to be synthesised using the methodology described in the *cytisine* subchapter. These Lupin alkaloids of our interest possess either a 2-methoxypyridine or a pyridone moiety. Unfortunately, as it was shown before, the very first step of the *cytisine* synthesis delivers low yields when 6-methoxypicoline is used as the starting material.

It had been attempted to change the first step of the *cytisine* synthesis to make it suitable for a methoxypyridine starting material. The α -arylation of malonates was reported and this transformation would have been desirable for our approach as it would have eliminated the need for bromopyridine to methoxypyridine conversion. This copper catalysed approach was reported for electron rich aromatic or pyridyl halides.⁸⁸ Additionally the synthesis of our compound of interest was described in a patent⁸⁹ involving the copper catalysed coupling of 2-bromo-6-methoxypyridine with diethyl malonate (Figure 133) followed by decarboxylation to the corresponding methoxypyridylacetic acid ester **2-65**.

Figure 133: Coupling with diethyl malonate (L=2-picolinic acid)

The yield of this two-step synthesis was reported to be 40% which is rather low for the initial steps for a linear total synthesis. This transformation was reproduced and only 37% conversion was obtained. It was decided to stick to the bromopyridine starting material due to the high initial yields.

Several approaches for installing the methoxypyridine or the pyridone moiety at different stages of the synthetic scheme will be described here. In general, our intermediates are limiting the

number of possible synthetic tools due to sensitive functional groups being present and because of this, different approaches were tested on different model systems. To explore all possibilities, the following direct approaches were considered using the leftover *N*-tosyl intermediates:

- Oxidation of *N*-alkylated pyridinium salts
- Dealkylation of 2-alkoxypyridines (not compatible with ester containing intermediates)
- S_NAr reactions of 2-halopyridines (not compatible with ester containing intermediates)
- Cross coupling reactions of 2-halopyridines (not compatible with vinyl iodide containing intermediates)
- Indirect approaches: cross coupling/oxidation sequences (not compatible with ester containing intermediates)

Initially, inspiration was drawn again from van Tamelen's cytosine synthesis where it was shown that *N*-alkylated quaternary pyridinium salts can be oxidised to the corresponding pyridones.^{14b} To see if this approach can be reproduced, some *N*-alkylated pyridinium salts were prepared and subjected to oxidation (Figure 134).

Figure 134: Quaternarisation using methyl iodide followed by oxidation

The quaternary pyridinium salts **2-137** and **2-138** were prepared using methyl iodide in acetone and isolated by filtration.⁹⁰ Oxidation using potassium hexacyanoferrate⁹¹ yielded the same product for both pyridinium salts. The 1H NMR spectrum showed 4 aromatic peaks and a methyl singlet at 3.55 ppm which does not correspond to the desired products but matches the

literature data of *N*-methylpyridone **2-139**.⁸⁵ This can be explained by over oxidation of the substituent in position 2 followed by the desired reaction.

The *N*-alkyl group was attempted to be changed to methoxymethyl, but the corresponding pyridinium salts were either not formed or couldn't be isolated in acceptable purity. It had to be concluded that unfortunately this approach was not suitable for the desired transformation.

Another option to install the pyridone moiety was the *O*-demethylation of methoxypyridine moieties. Although it was shown in Chapter 2.6.5 that the methoxypyridine substrates deliver low yields in the initial step of the synthesis sequence, the possibility had to be studied.

Figure 135: Demethylation yielding pyridone

A model substrate, 6-methoxy-2-picoline **2-140** was successfully demethylated using HBr in acetic acid.⁹² Unfortunately the yield was low and the conditions were harsh. Subjecting the same substrate to demethylation using cc. HCl in dioxane under MW irradiation did not yield the desired product.⁹³ Although it has just been shown that the demethylation approach can yield the desired pyridone moiety (Figure 135), it was set aside as a possible approach that may be used on late-stage intermediates.

The easiest direct method appeared to be a straightforward S_NAr reaction of 2-halopyridines. Since the whole *cytisine* synthesis was carried out using the bromopyridine series, this seemed convenient. As an initial approach, a late-stage intermediate **2-133** was heated with KOH in dioxane but no notable product was isolated presumably due to intramolecular tosyl transfer and elimination which will be discussed later. Subsequently, NMR experiments were carried

out using the same substrate with KOH in DMSO-*d*₆ but the desired pyridone **2-142** was not observed (Figure 136).

Figure 136: Attempted S_NAr reaction with KOH

Another approach was the reaction of the bromopyridine intermediates with NaOAc as reported by Gallagher.⁹⁴ Initially, an early stage intermediate **2-66** was subjected to Gallagher's conditions and the pyridone formation was observed, unfortunately along with competitive decarboxylation. Lowering the temperature resulted in no conversion (Figure 135).

Figure 137: Pyridone synthesis inspired by Gallagher

As this approach has actually delivered the desired pyridone, it was tested on a late-stage intermediate **2-113** as well. The crude ¹H NMR spectrum indicated the presence of the pyridone **2-142** although full conversion was not achieved, and the NMR spectrum was messy due to the starting material being a 1:1 mixture of diastereomers (Figure 138).

Figure 138: Late-stage pyridone formation

This approach was proven successful to yield the desired pyridone compound, but the reaction conditions were too harsh, and further methodologies have been tested. One possibility to carry out S_NAr reactions under milder conditions is the use of fluoropyridines. Since the S_NAr

reaction follows an addition-elimination mechanism, the rate determining step is the addition which has a higher rate in the case of a highly polarised C-F bond. It was decided not to start the synthesis over with a fluoropyridine starting material.

Milder reaction conditions were expected to be required when transition metal catalysed cross couplings were used for the transformation of bromopyridine intermediates.

It has been reported that 2-halopyridines undergo Pd catalysed cross coupling reactions with hydroxide or alkoxides using Buchwald ligands.⁹⁵ As these reactions were done on nucleosides which seemed more delicate substrates than ours, thus it seemed like a robust and promising procedure. These papers did not explain their choice of ligands (^tBuXPhos, Me₄^tBuXPhos), but some other ligands (SPhos, JohnPhos) were in stock in our laboratory, and these were all screened together for this transformation as a milder alternative to the direct S_NAr reaction with KOH described before.

Figure 139: Attempted cross coupling with hydroxide

These reactions did not give consistent conversions which was most probably due to the unreliable quality of the Pd-dba catalyst, but the obtained product was always the same according to the crude ¹H NMR spectra. The chemical shift of the tosyl groups changed significantly and additional peaks appeared in the 5-6 ppm region indicating C=C bonds. The multiplicity of these peaks could not be determined as they were overlapping. Unfortunately, these reactions were carried out on very small scale due to the limited amount of starting materials and the products were too polar for successful separation on column chromatography. With the limited amount of information present, an explanation has been proposed where the

hydroxymethyl group is deprotonated and initiates an intramolecular tosyl transfer reaction followed by base mediated elimination (Figure 140).

Figure 140: Proposed mechanism of a side reaction

Considering the unsuccessful nature of this approach it was decided that it is not suitable for our desired transformation. Moreover, the tosyl protecting group was changed to nosyl in the meantime, which is highly labile in the presence of nucleophiles.

Indirect methods were also tested involving a cross coupling followed by an oxidation reaction. One of these approaches was the possible Dakin oxidation⁹⁶ of the corresponding pyridyl-2-carbaldehyde, while a different possibility was the oxidation⁹⁷ of the corresponding pyridylboronic acid ester.

The aldehyde synthesis for the Dakin oxidation failed. A reported reductive carbonylation procedure was followed using Pd(dppp)Cl₂ as the catalyst with Et₃SiH, Na₂CO₃ in DMF under 45 psi of CO pressure, but only SM was recovered.⁹⁸ When the reaction conditions were changed to P^tBu₃ as a more electron rich ligand, DIPEA as a homogenous base, dioxane as the solvent and the temperature/pressure raised to 120°C/100 psi, dehalogenation was observed. No more conditions were explored for this approach, but a suitable ligand was identified for further cross coupling reactions which is able promote oxidative addition on these substrates.

Synthesis of pyridones using an arylboronation/oxidation sequence was reported.⁹⁹ Although the reported substrates are highly electron deficient, it was attempted with our substrates as well, using 6-bromopicoline as the model system. Following the reported procedure which uses

Pd(dppf)Cl_2 , $(\text{BPin})_2$, KOAc in DMSO at 80°C no product was obtained, only starting material recovered. Changing the ligand again to P^tBu_3 , 50% conversion was achieved but the product was not the desired one (Figure 141).

Figure 141: Attempted Miyaura coupling

Besides the desired Miyaura coupling, a sequential Suzuki reaction yielded a bipyrindyl byproduct **2-145**.¹⁰⁰ Unfortunately the Suzuki coupling could not be suppressed, not even with slow addition (6 h) of the picoline starting material or rigorously anhydrous conditions. This was rather surprising, because as reported by Miyaura himself, a weak base such as KOAc does not promote the competing Suzuki coupling. The only explanation would be that the system was not so rigorously anhydrous after all and a stronger base (such as hydroxide) activated the pyridylboronic ester towards the Suzuki coupling. These approaches were concluded unsuccessful.

The conversion of aryl halides to phenols was reported by Snapper using $\text{Pd}(\text{PPh}_3)_4$ and aq. NaHCO_3 in THF.¹⁰¹ When repeating this procedure with our bromopyridylacetic acid ethyl ester intermediate, only starting material was recovered.

A copper catalysed Ullmann-type coupling of aryl halides with alcohols was reported by Buchwald.¹⁰² To our delight, subjecting 6-bromopicoline to these conditions, the desired product 6-methoxypicoline was obtained. As this compound was already considered not suitable for the initial step of the total synthesis, a later stage intermediate had to be tested. Subjecting the next intermediate in line ethyl-2-(6-bromopyrid-2-yl)acetate **2-66** to the Ullmann reaction, complete decomposition was observed. Following this, a highly late-stage

intermediate **2-146** was successfully converted to the corresponding methoxypyridine compound **2-147** which concludes our approaches for this transformation (Figure 142).

Figure 142: Ullmann-type coupling (sealed tube, under air)

The compound used for this reaction was obtained via the denosylation of the alcohol intermediate described during the cytosine synthesis using K₂CO₃ and thiophenol in MeCN:DMF 4:1 at 40°C. Despite the harsh conditions of this Ullmann-type coupling, the reaction profile was clean. The moderate yield can be attributed to the small scale of this reaction, and the lack of optimisation at this stage. It is anticipated that shorter reaction time or lower temperature could improve the yield, which will be investigated later.

With the procedure in hand for the methoxypyridine conversion, the final intermediate stage has been reached for the total synthesis of *jussiaeiine A* (Figure 142).

The obtained methoxypyridine compound **2-147** at this point is one step away from the synthesis of *jussiaeiine A*, and also one step away from the formal synthesis of *kuraramine* and *isokuraramine*. The final methoxypyridine to pyridone conversion was reported by Honda earlier.²⁴

With the final intermediate in hand, the *N*-methylation was attempted. Due to the limited amount available of this compound, the diastereomers were not separated for these experiments. A reductive methylation was chosen to be the final step, as it is exclusively selective for amine *N*-alkylation and over alkylation is not possible as compared to when methyl iodide is used.

Figure 143: Total synthesis of further Lupin alkaloids

Initially, the same *N*-methylation approach was used that has been reported by our group during the synthesis of 5-hydroxysedamine.¹⁰³ This approach uses paraformaldehyde and formic acid in refluxing dioxane overnight. Both the bromopyridyl and methoxypyridyl substrates were tested under these conditions as some flexibility was present in terms of the order of the last two steps of the synthesis. Using this approach no signals in the ^1H NMR spectrum indicated the presence of *N*-methyl groups. These singlets were reported to appear at 2.30 and 2.34 ppm (*cis* and *trans*, respectively).²⁴

Another approach involved using formalin and sodium triacetoxyborohydride in acetonitrile at room temperature to have a homogenous formaldehyde source. After just 1 hour the desired singlets appeared in the crude NMR spectrum indicating the *N*-methylation. Although the reaction did not seem complete as several peaks were found in the 5-6 ppm region of the proton spectrum indicating the presence of unreduced imines or aminoacetals. Although the NMR spectrum was rather difficult to interpret due to the high number of compounds (SM, imine, methylated, all diastereomers) the methyl singlets appeared at the right chemical shift and it was concluded that this approach could be suitable for finishing the total synthesis of the target Lupin alkaloids (Figure 144).

Figure 144: spectrum of the crude N-methylated material

As all the final intermediate was used up for these reactions, this stage of the research was ceased with the high hope that the obtained ^1H NMR spectrum of the crude material contained the target natural product. Subsequently, the enantioselective synthesis of Lupin alkaloids was started instead of preparing a new batch of the racemic final intermediate due to time constraint of PhD funding.

2.7.4 Enantioselective Total Synthesis of Lupin Alkaloids

Our approach for the enantioselective synthesis was envisioned through a similar route as the racemic series, except the alkylation step made diastereoselective by changing the ester functionality to a chiral auxiliary.

Figure 145: Strategy for synthesis of the enantioselective series

As it can be seen, the optically pure precursor **2-105** would undergo diastereoselective alkylation followed by reductive oxazolidinone cleavage to yield the same alcohol intermediate **2-105** as the racemic series involved, but in an enantiopure fashion (Figure 145).

To the best of our knowledge, only two reported examples exist on the coupling of oxazolidinones with pyridylacetic acid derivatives, and only one of these reports studies the alkylation of the coupled compound.

Figure 146: A literature example of oxazolidinone coupling

In this reported example¹⁰⁴ (Figure 146) pyridylacetic acid was transformed into an active ester **2-152** with *N*-hydroxysuccinimide which was isolated then coupled with the oxazolidinone (deprotonated by KHMDS). The overall yield for this two-step process was 28% which is rather low for us, considering that this step is quite early in our linear synthesis sequence.

Figure 147: Oxazolidinone coupling followed by alkylation

In this reported approach¹⁰⁵ (Figure 147) the acid is activated via formation of a mixed anhydride **2-155** using pivaloyl chloride and reacted with the *N*-lithated oxazolidinone. The yield of the coupling process was reported to be 60% which is satisfactory. They have also reported the alkylation of the coupled product under the standard Evans conditions using LiHMDS in THF at -78°C.¹⁰⁶

The stereoselectivity of the alkylation was not discussed, no *dr* value was reported and only a yield for the product was claimed. The alkylated product was stated to have *S* configuration at the newly formed stereogenic centre but no *ee* value was reported even after oxazolidinone cleavage. When discussing the outcome of the stereoselective alkylation, the authors simply just followed the predictions of the Evans model and did not carry out any experimental determination of the configuration. It has to be noted that Evans himself never reported the stereoselective alkylation of pyridine containing compounds!

According to the Evans model¹⁰⁶, a strong chelation involving a Li cation in the enolate will block the free rotation of the chiral auxiliary, which results in shielding one face of the molecule, and alkylation can only occur from the opposite face, yielding *anti*-alkylated product (Figure 148).

Figure 148: The Evans chiral alkylation model

With these very limited literature examples in hand the enantioselective synthesis of our target Lupin alkaloids has been attempted. Based on the Evans model, (*S*)-oxazolidinone had to be used which was derived from L-phenylalanine.

Figure 149: Preparation of bromopyridylacetic acid

Starting from 6-bromopicoline, just as in the racemic series, the previously discussed bromopyridylacetic acid ethyl ester **2-66** was prepared. This had to be hydrolysed in order to be able to undergo coupling with the Evans oxazolidinone. Hydrolysis with lithium hydroxide in dioxane/water did not furnish any product, which was believed to be an issue of isolation. The product bromopyridylacetic acid **2-157** is a zwitterionic compound, which means that both excess base and acid can result in salt formation. Since the isoelectric point of this compound is unknown, quenching the hydrolysis mixture with excess aqueous acid was not an option. Instead an equimolar amount of trifluoroacetic acid (with respect to the LiOH used) was used to quench the reaction, which did not result in any salt formation of the product. It was isolated in 86% yield via simple water/chloroform extraction. This two-step synthesis of the acid

compound does not require column chromatography and can be carried out on 50 g scale under standard laboratory conditions (Figure 149).

The Evans oxazolidinone was prepared in two steps from (*S*)-phenylalanine. Reduction to the respective aminoalcohol **2-158** followed by condensation¹⁰⁷ with diethyl carbonate furnished the desired oxazolidinone **2-159** (Figure 150).

Figure 150: Oxazolidinone synthesis

With both the acid **2-157** and oxazolidinone **2-159** in hand, the coupling was attempted. At first a transamidation approach was tested on the ester substrate which was reported by Weinreb.¹⁰⁸ In this experiment the oxazolidinone was activated by the addition of AlMe_3 then mixed with the ester compound. Unfortunately, this was unsuccessful possibly to the weak nucleophilicity of the oxazolidinone or the coordination of the aluminium by the pyridine nitrogen, and the starting materials were recovered.

As the easiest activation method, formation of the acid chloride was attempted with both SOCl_2 and $(\text{COCl})_2$ but unfortunately the insoluble hydrochloride salt of the starting material precipitated out in all cases.

Figure 151: Coupling scheme

Coupling agents and bases which are commonly used in the literature for this transformation were tested along with reagents that were available in our laboratory. During the initial

screening stage DCC and CDI were tested as coupling agents with different bases and CDI seemed quite promising (Figure 151, Table 11).

Table 11: Summary of coupling conditions

activating agent	eq	base	eq	Conversion (%)
DCC	1.5	NaH	1	5
CDI	1.5	NaH	1	24
CDI	1.5	NaH	2	0
CDI	1.5	KO ^t Bu	1	42
CDI	1.5	LiHMDS	1	5
CDI	1.5	BuLi	1	52
CDI	1.5	KO ^t Bu	2	17
CDI	1.0	KO ^t Bu	1	53
CDI	1.2	KHMDS	1	0
CDI	1.0	KO ^t Bu	1	66*

*: Freshly purified KO^tBu was used

As it can be seen CDI was superior to DCC and by the appropriate choice of base and number of equivalents of the nucleophile and base, the yield reached an acceptable range. In terms of the base, *n*-BuLi and KO^tBu gave the best results, but the reaction proceeded more cleanly with KO^tBu. Sodium hydride did not give consistent results due to its unreliable quality. The highest conversion was achieved when freshly purified KO^tBu was used instead of the commercial THF solution. The conversion data was determined from the ¹H NMR spectrum of the crude material comparing the integrals of the oxazolidinone and the product. These conversion values translate to isolated yield values almost perfectly in all cases.

Figure 152: Interfering acid-base side reaction

The moderate yield of the coupling could be due to an unwanted acid-base background reaction. The byproduct of the active ester formation is imidazole with a pK_A of 18.6⁹ which is added to the deprotonated oxazolidinone that has a pK_A of 20.5, being a 100 times weaker acid than imidazole. According to this, protonation of the oxazolidinone salt can occur, deactivating the oxazolidinone towards the coupling reaction. It was attempted to remove imidazole from the reaction mixture by using a solvent in which it has poor solubility. Unfortunately, when running the coupling reaction in toluene, low conversion (33%) was observed. It would seem logical at this point to add an excess of base to the reaction, but the table of data shows it to be counterproductive (Figure 153).

Figure 153: Instability of the coupled product in the presence of base

The reason for the lower yield is the instability of these types of compounds towards base. As they possess a rather acidic α proton, deprotonation can lead to elimination of the oxazolidinone moiety leaving a highly reactive ketene intermediate **2-163** behind which is prone to runaway reactions resulting in decomposition.

⁹ The pK_a values provided were measured in DMSO and obtained from Evans (http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf)

As a conclusion, excess CDI would lower the yield due to introducing more acidic imidazole in the reaction mixture, besides the deprotonated oxazolidinone being able to react with CDI itself. An excess of the nucleophile would promote the ketene formation; thus it was decided that a strict 1 equivalent of each reagent is used in order to obtain the highest yield.

This reaction can be scaled up to 30 mmol. In case of bigger batches, the yield drops significantly possibly due to mass transfer effects during the oxazolidinone deprotonation. The formed salt precipitates out from THF forming a thick slurry which is difficult to stir and on bigger scales complete deprotonation might not occur.

The unreacted acid forms insoluble crystals once the crude product is obtained, and by washing with EtOAc this acid can be recovered via a simple filtration, while the rest of the crude product will be found in the filtrate. Unfortunately, this acid is only soluble in ethanol, and can not be resubmitted to the coupling reaction. It was impossible to determine if the obtained crystals are truly the acid or some sort of salt. The ^1H and ^{13}C NMR is slightly different from the acid obtained from hydrolysis, but the X-ray structure of these crystals show the acid compound forming a very strong 3D H-bond structure which could be the cause of insolubility and the slight change in the NMR chemical shifts.

From the filtrate the product and the unreacted oxazolidinone can be easily separated via column chromatography.

Another approach was tested for our transformation which describes the coupling of aliphatic carboxylic acids with oxazolidinones using EDCI and DMAP.¹⁰⁹ Unfortunately this was unsuccessful, even with the addition of Et_3N . Changing DMAP to HOBt or HOBt/ Et_3N did not result in product formation and the starting materials were recovered in each case.

Another approach was very promising for the coupling reaction which involved the formation of the mixed anhydride with pivaloyl chloride (Figure 154).¹⁰⁵

Figure 154: Coupling through mixed anhydride

The yield of this approach was comparable to the CDI coupling, but the whole procedure was troublesome to scale-up. As it was mentioned before, the oxazolidinone deprotonation yielded a thick slurry, and the CDI activated acid (which is a clear solution) was transferred to this slurry via cannula. When forming the mixed anhydride **2-164** with PivCl, triethylamine hydrochloride is formed as the by-product. This salt is not only insoluble in the reaction mixture and blocking the cannula on bigger scales, but is also acidic, which has a similar protonation effect as the imidazole before. Although in this case the hydrochloride is virtually insoluble in the solvent, thus slowing down the degree of oxazolidinone protonation (Figure 155).

Figure 155: Possible background acid-base reaction

Inert filtration of the $\text{Et}_3\text{N}\cdot\text{HCl}$ was attempted but the morphology of this precipitate does not allow easy filtration as the crystal size is very small and it goes through the sintered filter. Despite the technical difficulties of this approach, a screening was conducted on possible reaction conditions (Figure 154, Table 12).

Table 12: Table of reaction conditions (Figure 154)

base 1	base 2	t/h	conversion (%)
Et ₃ N	<i>n</i> -BuLi	1	26
Et ₃ N	<i>n</i> -BuLi	3	50
Et ₃ N	<i>n</i> -BuLi	16	65*
Et ₃ N	<i>n</i> -BuLi	16	30
LiHMDS	<i>n</i> -BuLi	16	0
NaHMDS	<i>n</i> -BuLi	16	23
KHMDS	<i>n</i> -BuLi	16	16

Reactions were carried out on 1 mmol scale at -78°C using 1 eq of each reagent. * 1 eq of acid and 2 eq of all other reagents

The best conversion achieved was 65% which translated to isolated yield. Considering all the difficulties, it was decided that the CDI method is more suitable for our purposes.

With the coupled alkylation precursor in hand, the stereoselective alkylation was attempted. The screened variables included bases, solvents and temperatures. Conversion values were determined from the ¹H NMR spectrum of the crude material comparing the integrals of product and SM signals (Figure 156, Table 13).

Figure 156: Alkylation scheme

Table 13: Summary of alkylation conditions

base	solvent	T/°C	t/h	conversion (%)	dr
LiHMDS	THF	-78 to 25	20	100	decomposition
LiHMDS	THF	-78	20	0	-
LiHMDS	THF	-60	20	0	-
NaHMDS	THF	-78	20	0	-
NaHMDS	THF	-60	20	0	-
KO ^t Bu	THF	-78	20	0	-
NaO ^t Bu	THF	-60	20	0	-
LiHMDS	DME/THF	-40	17	0	-
KO ^t Bu	PhMe/THF	-40	20	33	58:44
KHMDS	THF	-40	20	78	67:33
KO ^t Bu	THF	-40	20	70	67:33
NaHMDS	DME/THF	-40	17	55	69:31
KO ^t Bu	Pyr/THF	-40	20	88	70:30
KO ^t Bu	DME/THF	-40	20	81	72:28
KO ^t Bu	DME/THF	-50	20	78	73:27
KO ^t Bu	DMF/THF	-40	20	93	82:18
KO ^t Bu	DME/THF	-40	44	89	70:30
KO ^t Bu	DMF	-40	20	9	82:18

Analysis of the optimisation table shows very strong temperature, solvent and surprisingly cation dependence on the conversion and the diastereomeric ratio. There seems to be a well-defined activation barrier to the reaction somewhere between -60°C and -50°C and below -60°C absolutely no product is observed whatsoever. Considering conversion and *dr* the optimal

temperature was chosen to be -40°C which can be easily maintained using dry ice and acetonitrile.

In terms of the cation, any entry where a lithium base was used resulted in no product formation. When a sodium base was used at the appropriate temperature, the *dr* was comparable to the one obtained with potassium base, but the conversion dropped significantly. High conversion and *dr* were only obtained when a potassium base was used.

In terms of solvent, a very clear trend is observed. With the increased coordination ability of the solvent, the conversion and *dr* increased. Toluene gave poor conversion and *dr*, THF gave a significantly better result. DME was even better, pyridine increased the yield even more, and finally in DMF both the conversion and the *dr* was at the highest observed value. All these experiments were conducted in mixed solvent as the KO^tBu was a THF solution. When preparing a DMF solution of the base, no further improvement was obtained.

As strange as it is, this is the complete opposite effect of what the Evans model is based on. Diastereoselectivity originates in the Evans system from the conformational rigidity of the lithium chelated enolate which is formed because the lithium cation is actually able to coordinate to the enolate instead of being completely solvated by THF. In our case, a potassium cation gives the best results which is the weakest coordinating cation that has been tested. Moreover, the stronger coordinating solvent we use the better result we have. This all indicates that some other driving force is present in our system than in the Evans model.

Figure 157: Competing chelation

As it can be seen, a competing chelation is present in this system (Figure 157). When the metal cation is sitting between the enolate oxygen and the pyridine nitrogen, the chiral auxiliary can freely rotate along the C-N bond which can explain the relatively low diastereoselectivity (~4:1) obtained.

All these considerations made us raise the important question of whether our system actually gives the anticipated stereochemistry which is predicted by the Evans model. To our delight, the major diastereomer was easy to separate from the minor one using simple silica column chromatography and it turned out to be a highly crystalline compound. To our great surprise, this major alkylation product had a *syn* geometry which is the opposite of the Evans prediction.

Figure 158 X-ray structure of the major alkylated product

As it can be seen in the X-ray structure, the product has the wrong stereochemistry (Figure 157). To the best of our knowledge, this is the first example of *syn* alkylation using the Evans chiral auxiliary. Since Evans worked on polyketides, he did not study pyridines at all.

Figure 159: Possible explanation of diastereoselectivity (arrows denote dipole vectors)

A hypothesis has been established to rationalise the unexpected stereochemistry. The pyridine nitrogen is a stronger Lewis acid than the carbonyl oxygen of the oxazolidinone, and the pyridyl chelate is favoured. This in itself would result in low diastereoselectivity, but increasing the polarity of the solvent will increase the *dr* as well. If the dipole moment of the chelate is considered, it can be seen that the one with the bigger dipole moment would lead to the *syn* alkylated product (anti-Evans). The increased polarity of the solvent results in stabilisation of this large dipole moment chelate, and this will serve as the driving force for stereoselectivity (Figure 159).

Another explanation for the relatively low diastereoselectivity could simply be an issue of epimerisation. If the alkylation proceeds slowly there is an ample amount of base present to deprotonate the alkylated product. In order to get evidence of possible epimerisation the diastereopure alkylated compounds were exposed to base.

In order to obtain the right enantiomers of our intermediates, the coupling and alkylation had to be repeated with the (*R*)-oxazolidinone under the exact same conditions as described before.

Figure 160: Epimerisation experiment

Upon treating the pure diastereomers with an equimolar amount of KO^tBu in THF for 1 hour at -40°C epimerisation was indeed observed. The major alkylation product (*syn* alkylated) suffered a great degree of epimerisation as the obtained *dr* was 56:44, while the minor product (*anti*) was obtained with a *dr* of 87:13. The significantly different rate of epimerisation indicates that indeed the *anti*-alkylated product is the kinetically stable one (based on steric considerations), and opens up a possibility to maybe further increase the *dr* of the alkylation reaction by shortening the reaction time (Figure 160).

With the alkylated product in hand, possessing the right stereochemistry, the oxazolidinone had to be cleaved in order to access the enantiopure alcohol intermediate. Once this alcohol was prepared, the same synthetic scheme had to be used as before in the racemic series in order to obtain the target natural products.

The reductive cleavage of the oxazolidinone auxiliary yielding an alcohol has been reported by Evans himself.¹⁰⁶ According to the original report, 3 equivalents of LiAlH₄ in THF at 0°C furnishes the corresponding alcohol without racemisation. The issue of racemisation arises due to the acidic α -proton present in both the oxazolidinone containing compound and the aldehyde intermediate which requires the reaction to be ran in a controlled manner. Strict temperature

control and slow portion wise addition of LiAlH_4 is generally advised. Quenching of the reaction mixture has to be done carefully as well.

The reductive cleavage of this chiral auxiliary is a well-established procedure, often used in total synthesis, even in the case of substrates containing multiple chiral centres which are prone to epimerisation. Evans reported the use of LiBH_4 at -10°C during his total synthesis of Lonomycin A¹¹⁰; Smith has used NaBH_4 at 0°C for the synthesis of Calyciphylline N¹¹¹; Nicolaou cleaves his oxazolidinone using a Luche reduction with NaBH_4 and CeCl_3 at -30°C during his synthesis of a Maitotoxin fragment.¹¹²

For our delight the simplest method of reductive oxazolidinone cleavage was successful. Using LiAlH_4 in THF at 0°C under strict temperature control furnished the desired alcohol intermediate **2-176** with 95% *ee* based on ^{19}F NMR integral values (Figure 161, 162). The optical purity was determined through the corresponding Mosher's ester **2-177**.¹¹³ The yield of this reduction was 94% possibly due to changing the quenching agent from water to sat. aq. Na_2SO_4 which does not result in chunks of aluminium salts trapping the product which are usually observed when using water.

Figure 161: Oxazolidinone cleavage and Mosher's ester formation

With the chiral alcohol **2-176** in hand, the same synthetic scheme had to be carried out as discussed before in the case of racemic *cytisine*. Slight modifications were applied to certain steps of the synthesis.

Figure 162: (A): (*S*)-Mosher ester of the racemic alcohol; (B) and (C) (*S*)-Mosher ester of the optically enriched alcohol

The *aza*-Michael cyclisation precursor **2-180** was prepared from here through the same pathway as before. The alcohol **2-176** was subjected to the amide Mitsunobu reaction, where two equivalents of each reagent were used to increase conversion. In this case the product **2-178** co-elutes on the column with the remaining nosyl carbamate and can't be obtained as a pure compound. It was carried through to the deprotection step after which column chromatography yielded the pure sulphonamide **2-179**. This was followed by carbonylation where in order to speed up the reaction, a slight heating was used.

Figure 163: Synthesis of the optically pure cyclisation precursor

The *aza*-Michael cyclisation was performed under thermodynamic conditions, but the amount of material was unfortunately too low at this point, so the diastereomers were not separated to avoid further loss of material. The mixture of *cis* and *trans* compounds was carried forward. It was reduced to the corresponding alcohol mixture **2-182** then converted to the corresponding mesylates. The intramolecular $\text{S}_{\text{N}}2$ cyclisation – hydrolysis sequence was performed yielding *N*-nosylcytisine **2-185** and the recovered *trans* mesylate **2-184**. This cyclisation was carried out in CDCl_3 as the reaction can not be monitored by TLC. Since the *cis* and *trans* mesylates have the same R_f , there will always be a starting material spot on the TLC plate. By running the reaction in the deuterated solvent, an aliquot can be analysed directly by ^1H NMR to monitor the disappearance of one of the mesyl peaks. Since the formed pyridinium salt intermediate precipitates out from the reaction mixture, the true disappearance can be observed. The final deprotection step was carried out, yielding *cytisine* **2-186** (Figure 164).

Figure 164: Total synthesis of cytosine

The optical rotation of the obtained material **2-186** was found to be -72° (c 0.5, CHCl₃) which matches the data reported in the literature: -76° (c 1.0, CHCl₃).¹¹⁴ With this, the total synthesis of (-)-cytosine was completed in 13 linear steps with an overall yield of 6%.

Certain steps in the enantioselective series proceeded with lower yield than in the racemic case, which was due to handling a much smaller amount of material, and also due to the time pressure to finish this synthesis on time for this dissertation to be submitted.

2.8 Conclusion and Summary

The established methodology was proven successful by completing the total synthesis of (-)-*cytisine* which matched up to the existing total synthetic approaches both in terms of overall yield and number of steps. It is not the shortest reported synthesis however, which is due to its stereodivergent nature that would allow us to complete the synthesis of further Lupin alkaloids. These alkaloids were not prepared during the work leading to this dissertation, but the final intermediate was accessed and only one last *N*-methylation step has to be completed in order to achieve the total synthesis of (+)-*jussiaeiine A* along with the formal syntheses of (+)-*kuraramine* and (+)-*isokuraramine*.

As it will be discussed in the next section, the developed methodology has potential for the totalsynthesis of further Lupin alkaloids which bear higher structural complexity.

In this current approach several cyclisation strategies were explored to access the 3,5-disubstituted piperidine moiety. Most of these strategies did not yield the desired products, but provided us with interesting insight into pyridine chemistry and with several heterocyclic by-products that could be of pharmaceutical interest.

During the total synthesis of *cytisine*, an unprecedented example was shown for a diastereoselective alkylation which does not follow the Evans model, and this was proven by X-ray data, a hypothesis, and experimental evidence of actually preparing the natural enantiomer of *cytisine*. The key step *aza*-Michael cyclisation gives the true stereodivergent nature of the approach as it can furnish selectively the *cis* and *trans* 3,5-disubstituted piperidine moiety with moderate to good diastereoselectivity.

The nosyl protecting group was also utilised here as a good alternative to the tosyl group which was shown to be not compatible with the pyridone moiety due to similar reduction potentials resulting in a competitive reduction of the pyridone moiety during detosylation.

2.9 Future work

The established methodology for these simple Lupin alkaloids can be extended to more complex structures found in the same family bearing a quinolizine scaffold (Figure 165).

Figure 165: Quinolizine based Lupin alkaloids

The retrosynthetic analysis of these compounds shows that they are derived from a similar common intermediate as the alkaloids described in Chapter 2. By two C-N bond disconnections this structural relationship can be shown (Figure 166).

Figure 166: Retrosynthesis of quinolizine alkaloids

Thermopsine can be synthesised from *mamananine* using an intramolecular S_N2 reaction similar to the one which was described in the case of *cytisine*. Only in this example the pyridone would act as the nucleophile instead of the pyridine nitrogen, and base would be required. *Mamananine* and *jussiaeiine B* are interconvertible as the only difference between the two natural products is the methoxypyridine/pyridone moiety.

By disconnecting the C-N bond of the quinolizine in *mamanine*, an *N*-alkylation reaction visualises. By further disconnecting the C-N bond of the piperidine, an *aza*-Michael reaction arises where – in contrast to the previous example – two new chiral centres are being formed. The outcome of both the kinetic and the thermodynamic Michael additions remains to be seen.

Figure 167: Further retrosynthesis

It becomes clear that the only difference between the synthesis of these alkaloids and the previously described ones is in the higher structural complexity of the alkylating agent. This resembles a synthetic challenge, mostly because of the trisubstituted double bond which has to be prepared as both the *E* and *Z* alkene to ensure a proper screening of the *aza*-Michael reaction conditions.

In case of the *aza*-Michael cyclisation, not one but two new chiral carbons will be formed in a vicinal fashion. This would increase the number of possible diastereomers to be formed, but the steric effect of the sulphonamide group has to be considered as well. As it was shown in Chapter 1, any group α to the sulphonylated piperidine nitrogen will occupy an axial position due to the tosyl/nosyl group being pseudoequatorial. The pyridyl group would possibly stay equatorial, although as of now it is unknown how the axial α -substituent would interfere sterically, as it would be *cis* to the equatorial pyridyl group (Figure 168).

Figure 168: Possible *aza*-Michael cyclisation products

The alkylating agent for the synthesis of these alkaloids should have a leaving group which can be used for the alkylation; the vinyl iodide moiety for the carbonylation to introduce the Michael acceptor site; a surrogate leaving group for the late-stage *N*-alkylation mentioned before; and the backbone of the quinolizine B ring (Figure 169).

Figure 169: Possible alkylating agents for quinolizine alkaloid synthesis

To the best of our knowledge, none of these alkaloids have been synthesised before, and this would be the very first instance of achieving the total synthesis of a high number of Lupin alkaloids using the same strategy.

2.10 Experimental and Methods

Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware unless stated otherwise. Anhydrous DCM was freshly distilled from CaH₂ under nitrogen, anhydrous THF was freshly distilled from sodium metal and benzophenone under nitrogen, anhydrous toluene was freshly distilled from sodium metal under nitrogen. Anhydrous ethanol and methanol were distilled from activated magnesium under nitrogen. Anhydrous DMF was distilled from CaH₂. All chemicals were obtained from commercial sources and used as received otherwise noted. Column chromatography was carried out on silica gel, 230-400 mesh. Purity of the reported compounds was established by comparing the integrals of the peaks belonging to the compounds to the ones arising from impurities. NMR spectra were recorded on JEOL ECA400SL or JEOL ECA 400 spectrometers in CDCl₃ solutions unless stated otherwise. Chemical shifts are given in ppm and coupling constants in Hz (CDCl₃ ¹H: 7.26 ppm, ¹³C: 77.23 ppm). FTIR spectra were recorded on Shimadzu IRPrestige-21. Mass spectra were recorded on Thermo Scientific LCQ FLEET in ESI+ mode. High resolution MS were recorded on Waters UPLC-QTOF Premier. Optical rotations were measured on a Jasco P-1030 polarimeter using a 10 mm path-length cell at 589 nm.

Synthesis of 2-7 (Chapter 2.5)

2-phenylbut-3-en-1-ol (2-1): To a solution of styrene oxide (2.38 mL, 20.8 mmol) in Et₂O (69 mL) was added vinylmagnesium chloride (1.6 M in THF; 14.3 mL, 22.8 mmol) under N₂ and stirred for 1 h at room temperature. The mixture was quenched with sat. aq. NH₄Cl and extracted 3x with EtOAc. The combined organic layers were dried over anh. MgSO₄, filtered and concentrated. Column chromatography (hexane:EtOAc 95:5 to 90:10) gave **144** as a colourless liquid: 1.86 g (12.5 mmol), yield: 60%. Spectra in accordance with the literature: Lightburn, T.E.; Dombrowski, M.T.; Tan, K.L. *J. Am. Chem. Soc.* **2008**, *130*, 9210.

Methyl-(2-phenylbut-3-en-1-yl)(tosyl)carbamate (2-4): To a solution of methyl tosylcarbamate¹⁰ (2.63 g, 11.5 mmol), **2-1** (1.48 g, 10 mmol) and PPh₃ (3.02 g, 11.5 mmol) in THF (115 mL) under N₂ was added portionwise DIAD (2.26 mL, 11.5 mL) with external water cooling. The mixture was stirred at room temperature for 3 h then concentrated. Column chromatography (hexane:EtOAc 95:5 to 80:20) gave **2-4** as a colourless oil: 3.3 g (9.18 mmol), yield: 92%.

¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.23 (m, 7H), 6.08 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H), 5.19 – 5.10 (m, 2H), 4.21 – 4.09 (m, 2H), 3.89–3.80 (m, 1H), 3.60 (s, 3H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 153.1, 144.7, 141.0, 138.1, 136.7, 129.4 (2C), 128.8 (2C), 128.7 (2C), 128.2 (2C), 127.1, 117.5, 53.8, 51.8, 50.5, 21.8

4-methyl-N-(2-phenylbut-3-en-1-yl)benzenesulfonamide (2-5): A mixture of **2-4** (3.0 g, 8.34 mmol) and K₂CO₃ (1.5 g, 10.85 mmol) in MeOH was stirred at room temperature for 20 h then quenched with sat. aq. NH₄Cl and filtered. The filtrate was extracted 3x with EtOAc and the combined organics were dried on anh. MgSO₄, filtered and concentrated. Column chromatography (hexane:EtOAc 90:10 to 80:20) gave **2-5** as a white solid: 2.2 g (7.3 mmol), yield: 88%.

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.33 – 7.20 (m, 5H), 7.07 (d, *J* = 7.5 Hz, 2H), 5.89 – 5.79 (m, 1H), 5.14 (dd, *J* = 10.3, 1.0 Hz, 1H), 5.06 (dd, *J* = 17.2, 1.1 Hz, 1H), 4.43 – 4.35 (m, 1H), 3.39 (q, *J* = 7.5 Hz, 1H), 3.26 – 3.20 (m, 2H), 2.43 (s, 3H)

3-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine (2-7): In a Fischer-Porter flask **2-5** (2 g, 6.6 mmol), Rh₂(OA)_{c4} (8.7 mg, 0.02 mmol), BIPHEPHOS (31.2 mg, 0.041 mmol) were dissolved in anhydrous toluene (50 mL). The flask was charged with 30 psi of CO and 30 psi of H₂. The flask was purged with 60 psi of the gaseous mixture 4 times, then the pressure was set to 60 psi

¹⁰ Prepared by the method of Tomooka *et. al. Org, Lett.* **2006**, 8, 963.

again. The mixture was stirred at 85°C for 38 h, then the flask was cooled to ambient temperature and depressurized. The solvent was evaporated and the residue was purified with column chromatography (hexane: EtOAc 90:10). **2-7** was obtained as an off-white solid, 1.76 g (5.62 mmol), yield: 85%.

¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.18 (m, 5H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.11 (dt, *J* = 7.9, 3.9 Hz, 1H), 3.90 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.96 (t, *J* = 11.7 Hz, 1H), 2.74 – 2.63 (m, 1H), 2.43 (s, 3H), 2.18 – 2.11 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 143.9, 142.3, 135.2, 130.0 (2C), 128.9 (2C), 127.3 (2C), 127.2 (2C), 125.1, 108.4, 100.1, 49.4, 37.8, 28.9, 21.8; FTIR (neat, cm⁻¹) *v*_{max} 3419, 2852, 2725, 1645, 1467, 1161, 1097, 970, 682; MS (ESI+) *m/z* 314 (MH⁺, 100), 336 (MNa⁺, 25);

Chapter 2.6.2

2-(6-methoxypyridin-2-yl)but-3-en-2-ol (2-28): To a THF solution of vinylmagnesium chloride (3.97 mmol, 1.6 M) at 0 °C was added **2-27** (0.4 g, 2.65 mmol) in THF (2.6 mL) dropwise and stirred for 1 h. The mixture was quenched with sat. aq. NH₄Cl and extracted 3x with Et₂O. The combined organics were washed with brine then dried over anh. MgSO₄, filtered and concentrated. An orange oil was obtained, 0.431 g (2.4 mmol), yield 91%.

¹H NMR (396 MHz, CDCl₃) δ 7.59 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.11 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.6 Hz, 1H), 4.95 (brs, 1H), 3.96 (s, 3H), 1.61 (s, 3H).

The isomeric primary allylic alcohol: *(E)-3-(6-methoxypyridin-2-yl)but-2-en-1-ol*: ¹H NMR (400 MHz, CDCl₃) δ 7.62 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.73 – 6.64 (m, 2H), 4.45 (d, *J* = 6.6 Hz, 2H), 4.26 (s, 2H), 3.98 (s, 3H), 2.11 (s, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 162.9, 156.0, 140.2, 135.2, 130.3, 113.1, 109.0, 60.0, 53.9, 14.5.

(E)-2-(4-chlorobut-2-en-2-yl)-6-methoxypyridine (**2-29**): To a mixture of **2-28** (0.179 g, 1 mmol) and pyridine (0.096 mL, 1.2 mmol) in DCM (3mL) was added SOCl₂ (0.087 mL, 1.2 mmol) slowly and stirred for 50 min. The mixture was concentrated and DCM/H₂O was added and extracted 3x with DCM. The combined organics were washed with brine then dried over anh. MgSO₄, filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 95:5. A yellow oil was obtained, 108 mg (0.55 mmol), yield 55%.

¹H NMR (396 MHz, CDCl₃) δ 7.53 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.78 – 6.70 (m, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 4.32 (d, *J* = 8.1 Hz, 2H), 3.95 (s, 3H), 2.15 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.1, 155.5, 139.3, 139.0, 124.9, 113.0, 110.0, 53.2, 41.0, 14.5;

2-(6-methoxypyridin-2-yl)but-3-en-2-yl acetate (**2-30**): To a solution of **2-28** (0.56 g, 3.12 mmol) in Et₂O (15 mL) at 0 °C was added *n*-BuLi (3.44 mmol, 1.6 M) and the mixture was warmed up to 23 °C in 15 min. Acetyl chloride (0.245 mL, 3.44 mmol) was added slowly and the mixture was stirred for 17 h. . The mixture was quenched with sat. aq. NH₄Cl and extracted 3x with EtOAc. The combined organics were washed with sat. aq. NaHCO₃ then dried over anh. MgSO₄, filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 97:3. A colourless oil was obtained, 120 mg (0.54 mmol), yield 17%.

¹H NMR (396 MHz, CDCl₃) δ 7.52 (dd, *J* = 8.2, 7.4 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.38 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.23 (dd, *J* = 31.4, 14.2 Hz, 2H), 3.90 (s, 3H), 2.11 (s, 3H), 1.88 (s, 3H).

The primary allylic acetate isomer: *(E)*-3-(6-methoxypyridin-2-yl)but-2-en-1-yl acetate (**2-33**):

¹H NMR (396 MHz, CDCl₃) δ 7.53 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.70 – 6.59

(m, 2H), 4.85 (d, $J = 6.9$ Hz, 2H), 3.95 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.2, 163.1, 155.8, 139.2, 138.5, 123.7, 112.7, 109.7, 61.9, 53.1, 21.1, 14.5.

2-(6-methoxypyridin-2-yl)but-3-en-2-yl 2,2,2-trifluoroacetate (2-32): To a solution **2-28** (0.179 g, 1 mmol) and a catalytic amount of DMAP in Et_2O (3.5 mL) at 0 °C was added *n*-BuLi (1.2 mmol, 1.6 M) and warmed to 23 °C over 15 min. Trifluoroacetic anhydride (0.17 mL, 1.2 mmol) was added slowly and the mixture was stirred for 2 h. The mixture was quenched with sat. aq. NaHCO_3 and extracted 3x with EtOAc. The combined organic layers were washed with brine then dried over anhydrous MgSO_4 , filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 98:2. A yellow oil was obtained, 57 mg (0.21 mmol), yield 21%.

^1H NMR (396 MHz, CHCl_3) δ 7.55 (dd, $J = 8.1, 7.5$ Hz, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 6.73 – 6.63 (m, 2H), 5.10 (d, $J = 7.2$ Hz, 2H), 3.95 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, CHCl_3) δ 163.2, 155.1, 141.4, 139.2, 120.6, 113.1, 110.5, 65.2, 53.3, 14.6.

6,6'-(1-vinylcyclohex-3-ene-1,3-diyl)bis(2-methoxypyridine) (2-34): A mixture of **2-33** (0.07 g, 0.31 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.036 g, 0.03 mmol) in toluene (1 mL) was stirred at 23 °C for 15 min, then DIPEA (0.165 mL, 0.95 mmol) was added and the reaction was heated to reflux for 3 days, then concentrated. The crude product was purified by column chromatography using hexane:EtOAc 98:2. A yellow oil was obtained, 22 mg (0.07 mmol), yield 45%.

^1H NMR (396 MHz, CDCl_3) δ 7.48 (t, $J = 7.8$ Hz, 2H), 7.00 – 6.93 (m, 1H), 6.91 – 6.84 (m, 2H), 6.61 – 6.48 (m, 2H), 6.06 (dd, $J = 17.5, 10.7$ Hz, 1H), 5.07 (dd, $J = 27.1, 14.1$ Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.94 (d, $J = 18.4$ Hz, 1H), 2.67 – 2.57 (m, 1H), 2.53 – 2.39 (m, 3H), 2.16 – 2.05 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.4, 163.3, 163.1, 155.7, 144.4, 138.9, 138.8, 135.2, 126.5, 113.6, 113.2, 111.4, 108.6, 107.8, 53.2, 53.1, 46.0, 34.6, 31.7, 23.7.

Chapter 2.6.3

(1*E*,2*E*)-1,2-bis(1-(6-methoxypyridin-2-yl)ethylidene)hydrazine (**2-37**): To a mixture of iodine (0.533 g, 2.1 mmol) in THF (5 mL) at 23°C was added slowly TMG (0.5 mL, 4 mmol) followed by slow addition of **2-36** (0.165 g, 1 mmol) in THF (5 mL). The mixture was stirred for 15 min and sat. aq. Na₂S₂O₃ was added. The mixture was extracted 3x with EtOAc and the combined organics were washed with brine, dried over anh. MgSO₄, filtered and concentrated. A yellow solid was obtained, 145 mg (0.48 mmol), yield 96%.

¹H NMR (396 MHz, CDCl₃) δ 7.29 – 7.23 (m, 1H), 7.19 (dd, *J* = 8.7, 7.2 Hz, 1H), 6.19 (d, *J* = 7.2 Hz, 1H), 4.20 (s, 1H), 2.62 (s, 1H).

Chapter 2.6.4

3-(6-methoxypyridin-2-yl)-2,5-dihydrothiophene 1,1-dioxide (**2-48**): A mixture of 2-iodo-6-methoxypyridine **2-47** (0.235 g, 1 mmol), sulfolene (0.124 g, 1.05 mmol), Et₃N (0.174 mL, 1.2 mmol), Pd(OAc)₂ (0.011 g, 0.05 mmol) and tetra-*n*-butylammonium bromide (0.322 g, 1 mmol) in toluene (1 mL) was heated to 60°C for 16 h. The mixture was concentrated and purified by column chromatography using hexane:EtOAc 1:1. A yellow oil was obtained, 70 mg (0.31 mmol), yield 31%.

¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 8.1, 7.6 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 4.24 (dd, *J* = 3.3, 1.6 Hz, 2H), 4.09 – 4.04 (m, 2H), 3.93 (s, 3H).

Chapter 2.6.5

4-methyl-*N*-(2-(pyridin-2-yl)pent-4-yn-1-yl)benzenesulfonamide (**2-54**): A mixture of **2-53**⁵⁶ (0.89 g, 5.52 mmol), *N*-tosyl methylcarbamate (1.45 g, 6.35 mmol), PPh₃ (1.66 g, 6.35 mmol) and DIAD (1.25 mL, 6.35 mmol) in THF (70 mL) was stirred at 23°C for 2 h then concentrated. The product was isolated by column chromatography using hexane:EtOAc 95:5. A colourless oil was obtained which was contaminated with 14% reduced DIAD, 1.84 g (4.95 mmol)

^1H NMR (400 MHz, CDCl_3) δ 8.62 (d, J = 4.4 Hz, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.7 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.21 – 7.13 (m, 1H), 4.29 (dd, J = 14.4, 7.0 Hz, 1H), 4.20 – 4.10 (m, 1H), 3.54 (d, J = 1.0 Hz, 4H), 2.74 (dd, J = 4.8, 3.7 Hz, 2H), 2.42 (s, 3H), 1.26 (dd, J = 7.9, 7.1 Hz, 1H).

The obtained material (1.84 g, 4.95 mmol) and K_2CO_3 (0.887 g, 6.4 mmol) in MeOH (50 mL) was stirred for 16 h at 23°C. Sat. aq. NH_4Cl was added, then filtered and washed with EtOAc. The filtrate was concentrated and the residue was partitioned between EtOAc/ H_2O and extracted 3x with EtOAc. The combined organic layers were washed with sat. aq. Na_2CO_3 , then dried over anh. MgSO_4 , filtered, and concentrated. A dark oil was obtained, 1.32 g, 4.2 mmol), yield 76% over 2 steps.

^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 4.3 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.62 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.23 – 7.09 (m, 2H), 5.71 (t, J = 6.1 Hz, 1H), 3.52 – 3.26 (m, 2H), 3.14 (qd, J = 7.2, 4.3 Hz, 1H), 2.58 – 2.52 (m, 2H), 2.41 (s, 3H), 1.94 (t, J = 2.7 Hz, 1H).

4-methyl-N-((3-methylindolizin-1-yl)methyl)benzenesulfonamide (2-56): A mixture of **2-54** (0.05 g, 0.16 mmol) and $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$ (0.0125 g, 0.032 mmol) in DCE (1.2 mL) was heated to 70 °C for 7 h, then filtered and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 3:1, 1:1, 1:3.

2-65 was obtained as a purple oil, 2 mg (0.0063 mmol), yield 4%.

^1H NMR (396 MHz, CDCl_3) δ 7.76 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.1 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 1H), 6.64 – 6.58 (m, 1H), 6.55 – 6.50 (m, 1H), 6.34 (s, 1H), 4.40 – 4.24 (m, 3H), 2.45 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.5, 137.2, 130.3, 129.8, 127.4, 121.9, 119.6, 116.9, 116.0, 113.2, 110.5, 105.9, 39.5, 21.7, 11.5

2-55 was obtained as a yellow oil, 4 mg (0.012 mmol), yield 7%.

^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, J = 3.4 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 5.87 (brs, 1H), 3.60 – 3.44 (m, 1H), 3.31 (ddd, J = 13.5, 7.7, 5.8 Hz, 1H), 3.19 (dt, J = 12.4, 4.2 Hz, 1H), 3.09 – 2.80 (m, 2H), 2.40 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.9, 161.7, 149.1, 143.2, 137.1, 137.0, 129.7, 127.1, 123.7, 122.2, 46.2, 45.9, 40.2, 30.5, 21.5

Synthesis of 2-67 (analogous scheme to 2-54)

To a mixture of 2-methoxy-6-methylpyridine (1.5 g, 12.31 mmol) and diethyl carbonate (4.47 mL, 36.9 mmol) in THF (30 mL) at -78°C was added LDA in THF (25.25 mmol) and the mixture was stirred at -78°C for 1 h then warmed to 23°C and stirred for 30 min. The mixture was quenched with sat. aq. NH_4Cl and extracted 3x with EtOAc. The combined organic layers were washed with brine, then dried over anh. MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 9:1. A yellow oil was obtained, 374 mg (1.92 mg), yield 16%. ^1H NMR (396 MHz, CDCl_3) δ 7.52 (dd, J = 8.3, 7.3 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.90 (d, J = 1.1 Hz, 3H), 3.73 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H).

The obtained material (374 mg, 1.92 mmol) was cooled to -78°C in THF (3.6 mL) and LiHMDS solution in THF (2.1 mmol, 1 M) was added and stirred for 15 min. Propargyl bromide (2.11 mmol, 80 w/w% in PhMe) was added and the mixture was warmed up to 23°C overnight. The mixture was quenched with sat. aq. NH_4Cl and extracted 3x with EtOAc. The combined organic layers were washed with brine, then dried over anh. MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 95:5. A yellow oil was obtained, 318 mg (1.36 mmol), yield 71%. ^1H NMR (396 MHz, CDCl_3) δ 7.61 – 7.38 (m, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.72 – 6.57 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.91-3.89 (3, 4H),

2.98 (ddd, $J = 16.9, 7.6, 2.7$ Hz, 1H), 2.85 (ddd, $J = 16.8, 7.5, 2.6$ Hz, 1H), 1.94 (t, $J = 2.7$ Hz, 1H), 1.23 (t, $J = 5.4$ Hz, 3H).

The obtained material (318 mg, 1.36 mmol) was cooled to 0 °C in Et₂O (7 mL) and LiAlH₄ (104 mg, 2.73 mmol) was added in portions over 1 h. The reaction was quenched by careful addition of water, dried with anh. MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 95:5. A colourless oil was obtained, 128 mg (0.67 mmol), yield 47%. ¹H NMR (396 MHz, CDCl₃) δ 7.55 (t, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 7.2$ Hz, 1H), 6.66 (d, $J = 8.3$ Hz, 1H), 4.08 – 3.97 (m, 2H), 3.90 (s, 3H), 3.07 – 2.97 (m, 1H), 2.78 – 2.69 (m, 1H), 2.63 (ddd, $J = 16.9, 7.3, 2.6$ Hz, 1H), 1.99 (t, $J = 2.7$ Hz, 1H).

The obtained material (128 mg, 0.67 mmol), *N*-methyl tosylcarbamate (176 mg, 0.77 mmol), PPh₃ (202 mg, 0.77 mmol) and DIAD (0.15 mL, 0.77 mmol) in THF (8.5 mL) was stirred at 23 °C for 2 h then concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15. A colourless oil was obtained, 214 mg (0.53 mmol), yield 80%. ¹H NMR (396 MHz, CDCl₃) δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.48 (dd, $J = 8.3, 7.2$ Hz, 1H), 7.27 (d, $J = 8.2$ Hz, 2H), 6.77 (d, $J = 7.1$ Hz, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 4.29 – 4.16 (m, 2H), 3.93 (s, 3H), 3.35 (s, 3H), 3.48 – 3.36 (m, 1H), 2.74 – 2.67 (m, 2H), 2.42 (s, 3H), 1.92 (t, $J = 2.6$ Hz, 1H).

The obtained material (214 mg, 0.53 mmol) and K₂CO₃ (96 mg, 0.69 mmol) in MeOH (5.5 mL) was stirred for 16 h then concentrated. The residue was partitioned between EtOAc/sat. aq. NH₄Cl abs extracted 3x with EtOAc. The combined organic layers were washed with brine, then dried over anh. MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15. A yellow oil was obtained, 142 mg (0.41 mmol), yield 78%. ¹H NMR (396 MHz, CDCl₃) δ 7.69 (d, $J = 8.2$ Hz, 2H), 7.49 (t, $J = 7.9$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 6.69 (d, $J = 7.2$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 5.50 (t, $J = 6.1$

Hz, 1H), 3.83 (s, 3H), 3.39 (t, $J = 6.3$ Hz, 2H), 3.10 – 2.84 (m, 1H), 2.54 (dt, $J = 7.2, 2.4$ Hz, 2H), 2.42 (s, 3H), 1.95 (t, $J = 2.6$ Hz, 1H).

Synthesis of 2-68 (analogous scheme to **2-54** and **2-67**)

To a solution of diisopropylamine (15.4 mL, 110 mmol) in THF (30 mL) was added *n*-BuLi (71 mL, 107.5 mmol, 1.52 M) at -78°C and stirred for 1 h. To the prepared LDA solution was cannulated a chilled mixture of 2-bromo-6-methylpyridine (5.69 mL, 50 mmol) and diethyl carbonate (12.1 mL, 100 mmol) in THF (100 mL) while maintaining the temperature below -60°C . The mixture was stirred at -40°C for 16 h then quenched with 200 mL sat. aq. NH_4Cl solution. The mixture was extracted with 4x50 mL EtOAc and the combined organic layers were washed with 100 mL brine and dried over anhydrous MgSO_4 , then filtered and concentrated *in vacuo*. The crude product was purified via column chromatography using hexane:EtOAc 4:1. The product was obtained as a yellow liquid: 12.1 g (quantitative).

^1H NMR (396 MHz, CDCl_3) δ 7.52 (t, $J = 7.7$ Hz, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 2H), 1.27 (t, $J = 7.1$ Hz, 3H)

The obtained material (2.187 g, 9 mmol) was cooled to -78°C in THF (15 mL) and LiHMDS solution in THF (9.45 mmol, 1 M) was added and stirred for 15 min. Propargyl bromide (9 mmol, 80 w/w% in PhMe) was added and the mixture was warmed up to 23°C overnight. The mixture was quenched with sat. aq. NH_4Cl and extracted 3x with EtOAc. The combined organic layers were washed with brine, then dried over anhydrous MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15. A yellow oil was obtained, 2.2 g (7.82 mmol), yield 87%. ^1H NMR (400 MHz, CDCl_3) δ 7.53 (t, $J = 7.7$ Hz, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.31 (d, $J = 7.4$ Hz, 1H), 4.20 (q, $J = 7.0$, 2H), 3.98 (t, $J = 7.5$ Hz, 1H), 2.96 (ddd, $J = 16.8, 7.2, 2.6$ Hz, 1H), 2.86 (ddd, $J = 16.9, 7.7, 2.7$ Hz, 1H), 1.59 (t, $J = 1.7$ Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H).

The obtained material (2.2 g, 7.82 mmol) was cooled to 0 °C in Et₂O (40 mL) and LiAlH₄ (592 mg, 15.64 mmol) was added in portions over 1 h. The reaction was quenched by careful addition of water, dried with anh. MgSO₄, filtered, and concentrated. A yellow oil was obtained, 1.66 g (6.92 mmol), yield 88%. ¹H NMR (396 MHz, CDCl₃) δ 7.52 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 4.12 – 3.90 (m, 2H), 3.10 (tdd, *J* = 7.3, 5.5, 4.0 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.71 (ddd, *J* = 17.0, 7.1, 2.7 Hz, 1H), 2.63 (ddd, *J* = 16.9, 7.6, 2.7 Hz, 1H), 1.99 (t, *J* = 2.7 Hz, 1H).

The obtained material (1.66 g mg, 6.92 mmol), *N*-methyl tosylcarbamate (1.82 g, 7.96 mmol), PPh₃ (2.08 g, 7.96 mmol) and DIAD (1.56 mL, 7.96 mmol) in THF (85 mL) was stirred at 23 °C for 3 h then concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15. A colourless oil was obtained contaminated with reduced DIAD. ¹H NMR (396 MHz, CDCl₃) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 4.26 (dd, *J* = 14.5, 6.5 Hz, 1H), 4.15 (dd, *J* = 12.5, 5.8 Hz, 1H), 3.55 (s, 3H), 2.72 (dd, *J* = 7.3, 2.6 Hz, 2H), 2.43 (s, 3H), 1.93 (t, *J* = 2.6 Hz, 1H).

The obtained material and K₂CO₃ (882 mg, 6.39 mmol) in MeOH (42 mL) was stirred for 16 h then concentrated. The residue was partitioned between EtOAc/sat. aq. NH₄Cl and extracted 3x with EtOAc. The combined organic layers were washed with brine, then dried over anh. MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography using hexane:EtOAc 85:15. A yellow oil was obtained **2-68**, 1.516 g (3.85 mmol), yield 55 % over 2 steps.

¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 5.11 (t, *J* = 6.3 Hz, 1H), 3.37 (t, *J* = 7.1 Hz, 2H), 3.16 (dd, *J* = 13.0, 6.3 Hz, 1H), 2.63 – 2.47 (m, 2H), 2.43 (s, 2H), 1.97 (s, 1H).

2-39 and **2-70** : A mixture of **2-68** (100 mg, 0.25 mmol) and AgOAc (8.5 mg, 0.05 mmol) in DCE (2.5 mL) was stirred at 23 °C for 6 h then filtered and concentrated. The products were separated by column chromatography using hexane:EtOAc 9:1.

2-bromo-6-(5-methyl-1-tosyl-2,3-dihydro-1H-pyrrol-3-yl)pyridine (2-69) was obtained as a colourless oil, 44 mg (44% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.30 – 7.23 (m, 3H), 7.23 (s, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 5.00 (dd, *J* = 2.6, 1.3 Hz, 1H), 4.20 (dd, *J* = 11.4, 10.6 Hz, 1H), 4.00 (dd, *J* = 11.4, 5.5 Hz, 1H), 3.97 – 3.89 (m, 1H), 2.41 (s, 3H), 2.30 – 2.06 (m, 3H).

6-bromo-1'-tosyl-1',2',3',4'-tetrahydro-2,3'-bipyridine (**2-70**) was obtained as a colourless oil, 14 mg (14% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.09 (ddd, *J* = 8.0, 5.2, 2.6 Hz, 1H), 4.00 – 3.80 (m, 1H), 3.20 (dd, *J* = 11.9, 10.4 Hz, 1H), 3.02 – 2.82 (m, 1H), 2.44 (s, 3H), 2.41 – 2.28 (m, 1H), 2.23 – 2.12 (m, 1H).

Chapter 2.7.3

(5-(6-bromopyridin-2-yl)piperidin-3-yl)methanol **2-146**: A mixture of **2-182** (1:1 *dr*) (91 mg, 0.2 mmol), K₂CO₃ (83 mg, 0.6 mmol) and thiophenol (0.061 mL, 0.6 mmol) was heated to 45 °C in MeCN:DMF 4:1 for 1 h. The mixture was cooled and transferred straight to a column eluting with DCM:MeOH:NH₃(aq) 85:15:1. A colourless oil was obtained, 30.7 mg (0.11 mmol), yield 56%, as a 1:1 mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (m, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 3.94 – 3.64 (m, 2H), 3.65 – 3.44 (m, 3H), 3.40 – 3.12 (m, 4H), 3.12 – 2.96 (m, 3H), 2.89 (ddd, *J* = 15.3, 7.8, 3.6 Hz, 1H), 2.83 – 2.66 (m, 1H), 2.51 (s, 4H), 2.46 – 2.32 (m, 1H), 2.22 – 1.76 (m, 4H), 1.46 (dd, *J* = 24.7, 12.3 Hz, 1H).

(5-(6-methoxypyridin-2-yl)piperidin-3-yl)methanol (**2-147**): A mixture of **2-146** (27.1 mg, 0.1 mmol, 1:1 *dr*), CuI (1.9 mg, 0.01 mmol), 1,10-phenantroline (3.6 mg, 0.02 mmol) and Cs₂CO₃ (65 mg, 0.2 mmol) in MeOH was heated to 110 °C in a sealed tube under an atmosphere of air for 16 h. The mixture was cooled to room temperature, concentrated and purified by column chromatography using DCM:MeOH:NH₃(aq) 95:5:1. A yellow oil was obtained, 23 mg (quantitative). ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.42 (m, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.57 (t, *J* = 7.7 Hz, 2H), 4.37 (s, 4H), 3.91 (s, 3H), 3.89 (s, 3H), 3.80 – 3.69 (m, 2H), 3.59 (dd, *J* = 10.9, 4.8 Hz, 2H), 3.54 – 3.40 (m, 2H), 3.37 (d, *J* = 11.6 Hz, 1H), 3.20 (d, *J* = 9.8 Hz, 2H), 3.13 (d, *J* = 3.2 Hz, 2H), 2.96 (dd, *J* = 15.9, 7.4 Hz, 1H), 2.87 (t, *J* = 11.7 Hz, 1H), 2.63 (q, *J* = 7.2 Hz, 1H), 2.47 (t, *J* = 11.8 Hz, 1H), 2.21 – 1.76 (m, 4H), 1.48 (q, *J* = 12.8 Hz, 1H).

Chapter 2.7.4

ethyl 2-(6-bromopyridin-2-yl)acetate 2-66: To a solution of diisopropylamine (15.4 mL, 110 mmol) in THF (30 mL) was added nBuLi (71 mL, 107.5 mmol, 1.52 M) at -78°C and the mixture was stirred for 1 h. To the prepared LDA solution was cannulated a chilled mixture of 2-bromo-6-methylpyridine (5.69 mL, 50 mmol) and diethyl carbonate (12.1 mL, 100 mmol) in THF (100 mL) while maintaining the temperature below -60°C. The mixture was stirred at -40°C for 16 h then quenched with 200 ml sat. aq. NH₄Cl solution. The mixture was extracted with 4x50 mL EtOAc and the combined organic layers were washed with 100 mL brine and dried over anh. MgSO₄, then filtered and concentrated *in vacuo*. The crude product was purified via column chromatography using hexane:EtOAc 4:1. The product was obtained as a yellow liquid: 12.1 g (quantitative).¹¹

¹H NMR (396 MHz, CDCl₃) δ 7.52 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 155.8, 141.6, 139.0, 126.7, 123.0, 61.3, 43.4, 14.3; FTIR (neat, cm⁻¹) *v*_{max} 3084, 2983, 1732, 1581, 1556, 1435, 1176, 1118, 1028; MS (ESI+) *m/z* 244 (MH⁺, 100), 246 (MH⁺, 97); HRMS calcd for C₉H₁₁BrNO₂ (MH⁺, ⁷⁹Br) 243.9973; found 243.9982. HRMS calcd for C₉H₁₁BrNO₂ (MH⁺, ⁸¹Br) 245.9953; found 245.9960.

2-(6-bromopyridin-2-yl)acetic acid 2-157: **2-66** (47.15 g, 194 mmol) and LiOH•H₂O (8.15 g, 194 mmol) was stirred in a 1:1 mixture of dioxane/H₂O (250 mL) for 40 min at 25°C. Trifluoroacetic acid (14.85 mL, 194 mmol) was added and the mixture was stirred for another 30 min. The solvent was evaporated then H₂O (100 ml) was added and extracted with 3x50 ml DCM. The combined organic layers were washed with brine and dried over anh. MgSO₄, then filtered and concentrated *in vacuo*. The crude product was grinded into fine powder under

¹¹ Characterisation data in accordance with Patent US2016/297762 A1

hexane then filtered, washed with diisopropyl ether and hexane. The obtained yellow solid was dried using suction. 35.4 g (164 mmol), 85%.

^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.56 (m, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 7.5$ Hz, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 155.1, 141.2, 139.6, 127.2, 123.1, 42.5; FTIR (neat, cm^{-1}) ν_{max} 3433, 2100, 1643, 1454, 1384, 634; MS (ESI+) m/z 216 (MH^+ , 68), 218 (MH^+ , 100); mp 84-86°C.

ethyl 2-(6-bromopyridin-2-yl)-4-iodopent-4-enoate 2-104: To a solution of **2-66** (3.77 g, 15.5 mmol) in THF (25 mL) at -78°C was added LiHMDS (16.3 mmol, 1M in THF) and stirred for 15 min. A solution of 3-bromo-2-iodoprop-1-ene (3.8 g, 15.5 mmol) in THF (14 mL) was added and the mixture was warmed up to 25°C overnight. It was quenched with sat. aq. NH_4Cl (20 mL), and extracted with 3x15 mL EtOAc. The combined organic layers were dried over anhyd. MgSO_4 then filtered and concentrated *in vacuo*. The resulting red oil was purified by column chromatography using hexane:EtOAc 90:10. A yellow oil was obtained, 4.25 g (10.4 mmol), yield: 67%.

^1H NMR (400 MHz, CDCl_3) δ 7.50 (t, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.27 (d, $J = 6.7$ Hz, 1H), 6.01 (d, $J = 1.4$ Hz, 1H), 5.66 (d, $J = 1.6$ Hz, 1H), 4.20 – 4.13 (m, 2H), 3.18 (dd, $J = 14.7, 7.1$ Hz, 1H), 3.06 (dd, $J = 14.9, 8.0$ Hz, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 158.2, 141.8, 139.0, 128.8, 127.1, 122.6, 107.1, 61.5, 52.5, 46.8, 14.3; FTIR (neat, cm^{-1}) ν_{max} 2981, 1643, 1556, 1435, 1242, 1126, 1018, 900, 769; MS (ESI+) m/z 410 (MH^+ , 100), 412 (MH^+ , 95); HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{BrINO}_2$ 409.9253, found 409.9236.

(R)-4-benzyl-3-(2-(6-bromopyridin-2-yl)acetyl)oxazolidin-2-one (R-2-160): **2-157** (4.3 g, 20 mmol) and CDI (3.24 g, 20 mmol) in THF (50 mL) was stirred for 1.5 h at 25°C. In another flask *(R)*-4-benzyloxazolidin-2-one (3.54 g, 20 mmol) was cooled to 0°C in THF (100 mL) and

KO^tBu¹² (20 mmol, 1M in THF) was added slowly and stirred for 1.5 h at 0°C. The solution of the activated acid was cannulated to the oxazolidinone salt solution at 0°C at warmed up to 25°C overnight. The mixture was quenched with sat. aq. NH₄Cl (100 mL), extracted with 4x50 mL EtOAc and washed with brine (50 mL). The combined organic layers were dried over anh. MgSO₄, than filtered and concentrated *in vacuo*. The crude product was diluted with EtOAc and the crystalline acid residue was filtered off. The filtrate was concentrated and purified with column chromatography using a gradient of hexane:EtOAc 85:15 to 73:30. Further elution with 50:50 allows the recovery of unreacted oxazolidinone. The product was obtained as a yellow solid, 4.95 g (13.2 mmol), yield 66%.

¹H NMR (396 MHz, CDCl₃) δ 7.54 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.17 (m, 6H), 4.71 (ddd, *J* = 10.5, 6.7, 3.2 Hz, 1H), 4.46 (dd, *J* = 22.6, 16.6 Hz, 2H), 4.28 – 4.17 (m, 2H), 3.37 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.79 (dd, *J* = 13.4, 9.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.3, 155.7, 153.5, 141.7, 139.0, 135.4, 129.6 (2C), 129.1 (2C), 127.5, 126.7, 123.5, 66.6, 55.6, 44.4, 38.0 ; FTIR (neat, cm⁻¹) *v*_{max} 2922, 2850, 1645, 1663, 1454, 1377, 530; MS (ESI+) *m/z* 375 (MH⁺, 100), 377 (MH⁺, 96); 397 (MNa⁺, 32), 399 (MNa⁺, 29); HRMS calcd for C₁₇H₁₆BrN₂O₃ (MH⁺, ⁷⁹Br) 375.0344; found 375.0340. HRMS calcd for C₁₇H₁₆BrN₂O₃ (MH⁺, ⁸¹Br) 377.0324; found 374.0326. mp 100-102 °C; [α]_D²¹ -179° (*c* 0.11, MeOH)

(*R*)-4-benzyl-3-((*S*)-2-(6-bromopyridin-2-yl)-4-iodopent-4-enoyl)oxazolidin-2-one **2-175**: To a solution of **R-2-160** (3.25 g, 8.66 mmol) in anh. DMF (40 mL) was added KO^tBu (8.66 mmol, 1M in DMF) at -40°C and stirred for 30 min. A solution of 3-bromo-2-iodoprop-1-ene (2.12 g, 8.66 mmol) in anh. DMF (10 mL) was added slowly and the mixture was stirred at -40°C for 16 h. The reaction was quenched with sat. aq. NH₄Cl (100 mL), extracted with 4x40 mL EtOAc, washed with 40 mL H₂O and 40 mL brine. The combined organic layers were dried over anh.

¹² Commercial KO^tBu was dissolved in dry THF and filtered to remove KOH under a nitrogen atmosphere. The solvent was removed under maintaining the inert atmosphere.

MgSO₄, than filtered and concentrated *in vacuo*. The crude product (*dr* 81:19 *syn:anti*) was purified with column chromatography using hexane:EtOAc 95:5 to 90:10.

Major diastereomer (**2-175**, *syn* alkylated; *S,R*): pale yellow crystals, 3.06 g (5.65 mmol), yield: 65%.

¹H NMR (396 MHz, CDCl₃) δ 7.53 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.21 (m, 3H), 7.16 (d, *J* = 6.4 Hz, 2H), 6.01 (d, *J* = 1.2 Hz, 1H), 5.73 (d, *J* = 1.3 Hz, 1H), 5.30 (t, *J* = 7.1 Hz, 1H), 4.78 (ddt, *J* = 9.8, 7.9, 3.2 Hz, 1H), 4.22 (t, *J* = 8.5 Hz, 1H), 4.13 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.43 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.31 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.90 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.69 (dd, *J* = 13.7, 9.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 158.7, 153.0, 141.5, 138.9, 135.6, 129.6 (2C), 129.3, 129.0 (2C), 127.4, 126.9, 124.1, 107.4, 66.4, 55.4, 51.2, 47.5, 37.6; FTIR (neat, cm⁻¹) *v*_{max} 2954, 2924, 2063, 1643, 1633, 1359, 1124, 1020, 914; MS (ESI+) *m/z* 541 (MH⁺, 87), 543 (MH⁺, 100); 563 (MNa⁺, 58), 565 (MNa⁺, 52); HRMS calcd for C₂₀H₁₉BrIN₂O₃ (MH⁺, ⁷⁹Br) 540.9624; found 540.9620. HRMS calcd for C₂₀H₁₉BrIN₂O₃ (MH⁺, ⁸¹Br) 542.9603; found 542.9609. mp 117-118 °C; [α]_D²¹ -42° (*c* 0.11, MeOH)

Minor diastereomer (*anti* alkylated; *R,R*): yellow oil, 466 mg (0.86 mmol), yield: 10%.

¹H NMR (396 MHz, CDCl₃) δ 7.49 (t, *J* = 7.7 Hz, 1H), 7.39 – 7.31 (m, 4H), 7.31 – 7.20 (m, 3H), 6.05 (d, *J* = 1.3 Hz, 1H), 5.74 (d, *J* = 1.5 Hz, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 4.72 (dtd, *J* = 8.5, 5.0, 3.4 Hz, 1H), 4.14 (d, *J* = 5.0 Hz, 2H), 3.42 – 3.30 (m, 2H), 2.95 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.83 (dd, *J* = 13.4, 9.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 158.1, 153.1, 141.7, 138.9, 135.6, 129.7 (2C), 129.3, 129.2 (2C), 127.5, 127.1, 124.0, 107.2, 66.4, 56.0, 51.0, 47.6, 38.0; FTIR (neat, cm⁻¹) *v*_{max} 2850, 2104, 1643, 1633, 1462, 1373, 1053, 526; MS (ESI+) *m/z* 541 (MH⁺, 100), 543 (MH⁺, 93); 563 (MNa⁺, 23), 565 (MNa⁺, 21); HRMS calcd for C₂₀H₁₉BrIN₂O₃ (MH⁺, ⁷⁹Br) 540.9624; found 540.9620. HRMS calcd for C₂₀H₁₉BrIN₂O₃ (MH⁺, ⁸¹Br) 542.9603; found 542.9613; [α]_D²¹ -108° (*c* 0.09, MeOH)

(*S*)-2-(6-bromopyridin-2-yl)-4-iodopent-4-en-1-ol **2-176**: To a solution of **2-175** (14.9 g, 27.5 mmol) in THF (150 mL) was added LiAlH₄ (2.1 g, 55 mmol) portion wise over 2 h at 0°C under a stream of N₂. The mixture was quenched by dropwise addition of sat. aq. NaSO₄ then filtered through celite and concentrated in vacuo. The crude product was purified by column chromatography using hexane:EtOAc 85:15. The product was obtained as a colourless oil, 9.51 g (26 mmol), yield: 94%.

¹H NMR (396 MHz, CDCl₃) δ 7.50 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 5.97 (d, *J* = 1.2 Hz, 1H), 5.68 (d, *J* = 1.4 Hz, 1H), 3.99 (dt, *J* = 11.1, 3.6 Hz, 1H), 3.89 (ddd, *J* = 11.1, 8.2, 5.4 Hz, 1H), 3.25 – 3.17 (m, 1H), 3.12 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.84 (ddd, *J* = 22.2, 14.3, 7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 141.7, 139.0, 128.5, 126.6, 123.0, 109.1, 64.2, 47.3, 47.0; FTIR (neat, cm⁻¹) *v*_{max} 3062, 2931, 2877, 1612, 1581, 1550, 1435, 1157, 1126, 1064, 1026, 902, 794, 740; MS (ESI+) *m/z* 367 (MH⁺, 100), 369 (MH⁺, 91); HRMS calcd for C₁₀H₁₂BrINO (MH⁺, ⁷⁹Br) 367.9147; found 367.9149; HRMS calcd for C₁₀H₁₂BrINO (MH⁺, ⁷⁹Br) 367.9147; found 367.9149; [α]_D²¹ +103° (*c* 0.13, MeOH)

Methyl (R)-(2-(6-bromopyridin-2-yl)-4-iodopent-4-en-1-yl)((2-nitrophenyl)sulfonyl) carbamate **2-178**: A solution of **2-176** (4.4 g, 12 mmol), PPh₃ (3.39 g, 13.2 mmol), DTAD (3.0 g, 13.2 mmol) and methyl ((2-nitrophenyl)sulfonyl)carbamate (3.37 g, 13.2 mmol) in THF (mL) was heated at reflux for 16 h then concentrated. The residue was dissolved in DCM (50 mL) and TFA (25 ml) was added. The mixture was stirred until TLC indicated the disappearance of DTAD/reduced DTAD (molybdate stain). The mixture was concentrated and the residue dissolved in DCM. It was washed with water and 2 M aq. NaOH, then the organic layer was dried over anh. MgSO₄, filtered and concentrated in vacuo. The crude product was purified via column chromatography using gradient elution of hexane:EtOAc 80:20, 65:35, 50:50. The product was obtained as a yellow oil and it was contaminated with the unreacted

nosyl carbamate. A portion of this material was carried through the next step without further purification

^1H NMR (396 MHz, CDCl_3) δ 8.35 – 8.29 (m, 1H), 7.82 – 7.68 (m, 3H), 7.49 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 6.00 (s, 1H), 5.64 (s, 1H), i 4.22 (dd, J = 14.8, 9.0 Hz, 1H), 4.11 (dd, J = 14.8, 5.7 Hz, 1H), 3.70 – 3.36 (m, 4H), 3.05 (dd, J = 14.3, 9.2 Hz, 1H), 2.86 (dd, J = 14.3, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.8, 152.4, 148.2, 142.2, 138.8, 134.9, 134.8, 132.8, 132.0, 128.7, 126.8, 127.7, 124.1, 108.0, 54.3, 51.6, 47.3, 47.0; MS (ESI+) m/z 610 (MH^+ , 100), 612 (MH^+ , 92);

(R)-N-(2-(6-bromopyridin-2-yl)-4-iodopent-4-en-1-yl)-2-nitrobenzenesulfonamide: A mixture of **2-178** (1.6 g, 2.62 mmol) and K_2CO_3 (0.471 g, 3.4 mmol) in MeOH (25 mL) was stirred for 2 h at 25°C until the opaque mixture turned clear and TLC indicated the consumption of starting material. The mixture was concentrated, then sat. aq. NH_4Cl was added and extracted 4x with EtOAc. The combined organic layers were dried over anh. MgSO_4 , filtered and concentrated. The product was obtained as a yellow oil, 1.4 g (2.54 mmol), yield: 67% over 2 steps.

^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 7.4 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 7.3 Hz, 1H), 5.94 (d, J = 1.3 Hz, 1H), 5.89 (t, J = 6.1 Hz, 1H), 5.67 (d, J = 1.5 Hz, 1H), 3.49 (qdd, J = 10.3, 7.1, 5.3 Hz, 2H), 3.31 (ddd, J = 15.0, 7.8, 4.3 Hz, 1H), 2.82 – 2.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.3, 148.1, 142.3, 139.0, 133.9, 133.7, 133.1, 131.2, 129.1, 127.1, 125.6, 123.2, 107.7, 48.3, 45.9, 45.3; FTIR coming; MS (ESI+) m/z 552 (MH^+ , 100), 554 (MH^+ , 89); 574 (MNa^+ , 20), 576 (MNa^+ , 17); HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{BrIN}_3\text{O}_4\text{S}$ (MH^+ , ^{79}Br) 551.9090; found 551.9083; $[\alpha]_{\text{D}}^{21} +34^\circ$ (c 0.12, MeOH)

methyl (R)-4-(6-bromopyridin-2-yl)-2-methylene-5-((2-nitrophenyl)sulfonamido)pentanoate
2-180: A solution of **2-179** (3.24 g, 5.87 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (206 mg, 0.29 mmol), and Et_3N

(1.65 mL, 11.7 mmol) in MeOH (58 mL) was stirred overnight at 25°C under 1 atm of CO. The mixture was concentrated and the residue was dissolved in CHCl₃ then washed with water and 2M aq. HCl. The organic layer was dried over anh. MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified via column chromatography using gradient elution of hexane:EtOAc 80:20, 60:40, 50:50. The product was obtained as a yellow oil, 2.7 g (5.57 mmol), yield: 95%.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.15 (s, 1H), 5.94 (t, *J* = 6.0 Hz, 1H), 5.47 (s, 1H), 3.75 (s, 3H), 3.55 – 3.38 (m, 2H), 3.26 (qd, *J* = 7.4, 4.4 Hz, 1H), 2.67 (qd, *J* = 13.8, 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 162.4, 148.1, 142.1, 139.0, 136.9, 133.8, 133.6, 132.9, 131.1, 128.6, 126.8, 125.6, 123.0, 52.2, 46.3, 45.0, 35.9; FTIR (neat, cm⁻¹) *v*_{max} 3233, 3097, 3024, 2951, 1714, 1697, 1633, 1583, 1537, 1435, 1359, 1122, 952, 731, 499; MS (ESI+) *m/z* 484 (MH⁺, 100), 486 (MH⁺, 89); HRMS calcd for C₁₈H₁₉BrN₃O₆S (MH⁺, ⁷⁹Br) 484.0178; found 484.0193; [α]_D²¹ +14° (*c* 0.17, MeOH)

methyl (3S,5R)-5-(6-bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxylate (cis-2-181): A mixture of **2-180** (1.0 g, 2.06 mmol) and DBU (0.154 mL, 1.03 mmol) in dioxane (20 mL) was heated to reflux for 2h and quenched with 2 mL of sat. aq. NH₄Cl. The mixture was extracted 3x with CHCl₃, then washed with water and brine. The combined organic layers were dried over anh. MgSO₄, filtered and concentrated. The product was obtained quantitatively as a mixture of diastereomers (63:37 *cis:trans*).

¹H NMR (400 MHz, CDCl₃) δ 8.07 – 7.96 (m, 1H), 7.77 – 7.67 (m, 2H), 7.68 – 7.61 (m, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 4.21 – 4.14 (m, 1H), 4.07 – 4.01 (m, 1H), 3.70 (s, 3H), 3.09 – 2.98 (m, 2H), 2.98 – 2.88 (m, 1H), 2.80 (tt, *J* = 12.1, 3.8 Hz, 1H), 2.43 – 2.31 (m, 1H), 1.93 (dd, *J* = 25.2, 12.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃)

δ 172.6, 162.0, 148.3, 142.2, 139.2, 134.0, 132.3, 132.0, 131.1, 127.0, 124.5, 121.6, 52.3, 50.0, 47.0, 43.2, 41.4, 32.9; MS (ESI+) m/z 484 (MH^+ , 100), 486 (MH^+ , 80); HRMS calcd for $C_{18}H_{19}BrN_3O_6S$ (MH^+ , ^{79}Br) 484.0178; found 484.0181.

methyl (3R,5R)-5-(6-bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxylate (trans-2-181): To a solution of **2-180** (600 mg, 1.24 mmol) in THF (12 mL) was added LiHMDS (1.24 mmol, 1 M) in THF at 0 °C and stirred for 40 h. The mixture was quenched with sat. aq. NH_4Cl , then extracted 3x with $CHCl_3$, then washed brine. The combined organic layers were dried over anh. $MgSO_4$, filtered and concentrated. The product was obtained quantitatively as a mixture of diastereomers (5:95 *cis:trans*)

1H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 1H), 7.77 – 7.67 (m, 2H), 7.67 – 7.60 (m, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.29 (d, $J = 7.5$ Hz, 1H), 4.09 (dd, $J = 12.6$, 3.5 Hz, 1H), 3.82 (dd, $J = 12.1$, 3.7 Hz, 1H), 3.67 (s, 3H), 3.44 – 3.19 (m, 3H), 2.93 – 2.77 (m, 1H), 2.31 (dt, $J = 13.7$, 4.0 Hz, 1H), 2.21 – 2.07 (m, 1H).

((3S,5R)-5-(6-bromopyridin-2-yl)-1-((2-nitrophenyl)sulfonyl)piperidin-3-yl)methanol 2-182: A mixture of **2-181** (*dr* 1:1) (1.06 g, 2.19 mmol) was cooled to 0 °C in THF (22 mL) and $LiAlH_4$ (0.166 g, 4.38 mmol) was added portion wise over 1 h. The mixture was quenched by careful addition of sat. aq. Na_2SO_4 solution and concentrated in vacuo. The crude product was purified by column chromatography using DCM:MeOH: NH_3 (aq) 95:5:1. The product was obtained as a yellow oil, 696 mg (1.52 mmol, *dr* 1:1), yield 70%.

1H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.93 (m, 2H), 7.75 – 7.66 (m, 4H), 7.66 – 7.60 (m, 2H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 3.6$ Hz, 1H), 7.33 (d, $J = 3.5$ Hz, 1H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 4.05 (t, $J = 11.5$ Hz, 2H), 3.95 – 3.75 (m, 3H), 3.65 (ddd, $J = 18.7$, 10.6, 5.2 Hz, 2H), 3.59 – 3.47 (m, 1H), 3.30 (dd, $J = 12.5$, 10.1 Hz, 1H), 3.17 (ddd, $J = 16.4$, 9.7, 4.4 Hz, 2H), 3.10 – 2.91 (m, 2H), 2.61 (t, $J = 11.9$ Hz, 1H), 2.07 (dt, $J = 15.3$, 7.1 Hz,

3H), 1.95 – 1.76 (m, 1H), 1.59 – 1.42 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 162.8, 145.7, 142.1, 142.0, 141.1, 139.2, 133.9, 133.8, 132.9, 132.2, 131.9, 131.2, 131.1, 131.0, 126.8, 126.7, 124.4, 124.3, 121.6, 65.2, 62.4, 50.4, 50.3, 48.8, 46.8, 43.6, 39.5, 38.9, 35.5, 33.0, 31.1; MS (ESI+) m/z 456 (MH^+ , 100), 458 (MH^+ , 92); HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{BrN}_3\text{O}_5\text{S}$ (MH^+ , ^{79}Br) 456.0229; found 456.0220.

N-nosyl (-)-cytisine **2-185**: A 1:1 diastereomeric mixture of **2-182** (0.392 g, 0.86 mmol) and Et_3N (0.18 mL, 1.3 mmol) in DCM (15 mL) was cooled to 0°C and mesyl chloride (0.08 mL, 1.03 mmol) was added slowly. After stirring the mixture for 1 h, water was added and extracted 3x with CHCl_3 . The combined organic layers were dried over anh. MgSO_4 , filtered and concentrated in vacuo. A white foamy material was obtained (0.308 g, 0.61 mmol). Yield 77%.

The obtained mixture of mesylates in CDCl_3 (12 mL) was heated to reflux for 6.5 h then cooled to room temperature. Sat. aq. Na_2CO_3 (10 mL) was added and the mixture stirred for 9 h at 23°C . The aqueous layer was extracted 3x with EtOAc , and the combined organic layers were dried over anh. MgSO_4 , filtered and concentrated in vacuo. The crude product was purified using column chromatography with $\text{CHCl}_3:\text{MeOH}:\text{NH}_3(\text{aq})$ 95:5:1. *N*-Nosyl cytisine **2-185** was obtained as an orange oil, 76 mg (0.2 mmol), yield: 33% (66% from the *cis* mesylate).

^1H NMR (400 MHz, CDCl_3) δ 7.73 – 7.63 (m, 2H), 7.61 – 7.51 (m, 2H), 7.21 (dd, $J = 9.1$, 6.8 Hz, 1H), 6.33 (d, $J = 9.1$ Hz, 1H), 6.02 (d, $J = 6.9$ Hz, 1H), 4.10 (d, $J = 15.8$ Hz, 1H), 3.97 (dddd, $J = 12.4$, 4.8, 3.7, 2.0 Hz, 1H), 3.84 (ddd, $J = 15.7$, 6.6, 1.0 Hz, 1H), 3.20 (dd, $J = 12.3$, 2.1 Hz, 1H), 3.18 – 3.08 (m, 2H), 2.56 (brs, 1H), 2.09 – 1.97 (m, 1H), 1.95 – 1.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.1, 147.9, 138.6, 133.8, 131.8, 131.6, 130.3, 124.0, 117.9, 105.5, 53.0, 51.8, 48.6, 34.4, 27.2, 25.3 ; FTIR (neat, cm^{-1}) ν_{max} 3439, 2292, 1645, 1454, 1373, 1056, 956; MS (ESI+) 376 (MH^+ , 52), 751 (2MH^+ , 100); HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_5\text{S}$ (MH^+ , ^{79}Br) 376.0967; found 376.0982; $[\alpha]_{\text{D}}^{22}$ -184° (c 0.95 CHCl_3)

The unreacted *trans* mesylate **2-184** was recovered from the column. 147 mg (0.29 mmol), yield: 94%.

^1H NMR (400 MHz, CDCl_3) δ 8.01 – 7.91 (m, 1H), 7.77 – 7.68 (m, 2H), 7.63 (d, $J = 7.2$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 4.46 – 4.29 (m, 2H), 3.87 (d, $J = 12.2$ Hz, 1H), 3.77 (d, $J = 13.0$ Hz, 1H), 3.30 – 3.15 (m, 3H), 2.39 (tt, $J = 7.5$, 3.9 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.01 – 1.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.0, 148.5, 142.1, 139.3, 134.1, 132.0, 131.5, 131.1, 126.9, 124.4, 121.8; FTIR (neat, cm^{-1}) ν_{max} 2852, 2358, 1581, 1519, 1155, 1060, 964, 723; MS (ESI+) m/z 534 (MH^+ , 100), 536 (MH^+ , 90); 556 (MNa^+ , 24), 558 (MNa^+ , 25); HRMS calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_7\text{S}_2$ (MH^+ , ^{79}Br) 534.0004; found 534.9998; $[\alpha]_{\text{D}}^{22}$ -37° (c 1.08 CHCl_3)

(-)-*cytisine* **2-186** : A mixture of *N*-nosyl (-)-*cytisine* **2-185** (70 mg, 0.186 mmol), thiophenol (0.057 mL, 0.56 mmol), and K_2CO_3 (77 mg, 0.56 mmol) in $\text{MeCN}:\text{DMF}$ 4:1 (5 mL) was heated to 45°C for 30 min. The mixture was cooled to room temperature and transferred to a silica column and purified using an eluent of $\text{CHCl}_3:\text{MeOH}:\text{NH}_3(\text{aq})$ 90:10:1. (-)-*cytisine* was obtained as a white crystalline compound, 34 mg (0.179 mmol); yield: 96%.

^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, $J = 8.8$, 6.7 Hz, 1H), 6.45 (d, $J = 8.9$ Hz, 1H), 6.00 (d, $J = 6.8$ Hz, 1H), 4.12 (d, $J = 15.6$ Hz, 1H), 3.90 (dd, $J = 15.6$, 6.6 Hz, 1H), 3.15 – 2.95 (m, 4H), 2.90 (br, 1H), 2.32 (br, 1H), 2.00–1.92 (m, 2H), 1.56 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 151.2, 138.9, 116.9, 105.1, 54.2, 53.2, 49.9, 35.8; FTIR (neat, cm^{-1}) ν_{max} 3279, 1643, 1537, 1155; MS (ESI+) m/z 191 (MH^+ , 100), 403 (2MNa^+ , 88); HRMS calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}$ (MH^+) 191.1184; found 191.1189; Mp: 151–153 $^\circ\text{C}$ (lit. 155 $^\circ\text{C}$); $[\alpha]_{\text{D}}^{21}$ -72° (c 0.5 CHCl_3) (lit $[\alpha]_{\text{D}}^{23}$ -76° (c 0.5 CHCl_3)).

2.11 References

1. Husemann; Marme, *Edinburgh Med. J.* **1862**, 7, 1025.
2. Ing, H. R., *J. Chem. Soc.* **1931**, 2195.
3. Murakoshi, I.; Kidoguchi, E.; Haginiwa, J.; Ohmiya, S.; Higashiyama, K.; Otomasu, H., *Phytochemistry* **1981**, 20, 1407.
4. Murakoshi, I.; Kidoguchi, E.; Haginiwa, J.; Ohmiya, S.; Higashiyama, K.; Otomasu, H., *Phytochemistry* **1982**, 21, 2379.
5. Maximo, P.; Lourenco, A., *J. Nat. Prod.* **2000**, 63, 201.
6. Prochasa, J. J.; Das, S.; Benowitz, N. L., *British Med. J.* **2013**, 347, 6.
7. Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaefer, E.; Rollema, H.; Lu, Y.; Mansbach, S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D.; O'Neill, B. T., *J. Med. Chem.* **2005**, 48, 3474.
8. Scharfenberg, G.; Benndorf, S.; Kempe, G., *Dtsch. Gesundheitsw.* **1971**, 26, 463.
9. Barlow, R. B.; McLead, L. J., *J. Pharmacol.* **1969**, 35, 161.
10. Reavill, C.; Walther, B.; Stoleran, I. P.; Testa, B., *Neuropharmacology* **1990**, 29, 619.
11. Kianbakht, S.; Hajiaghvae, R.; Salehabad, A. R., *Research Journal of Pharmacognosy* **2017**, 4, 59.
12. Philipova, I.; Stavrakov, G.; Vassilev, N.; Nikilova, R.; Shivachev, B.; Dimitrov, V., *J. Organomet. Chem.* **2015**, 778, 10.
13. Stead, D.; O'Brian, P., *Tetrahedron* **2007**, 63, 1885.
14. (a) van Tamelen, E. E.; Baran, J. S., *J. Am. Chem. Soc.* **1955**, 77, 4944; (b) van Tamelen, E. E.; Baran, J. S., *J. Am. Chem. Soc.* **1958**, 80, 4659.
15. Bohlmann, F.; Englisch, A.; Ottawa, N., *Chem. Ber.* **1956**, 89, 792.
16. Govindachari, T. R.; Rajadurai, S.; Subramanian, M.; Thyagarajan, B. S., *J. Chem. Soc.* **1957**, 3844.

17. Dixon, A. J.; McGrath, M. J.; O'Brian, P., *Org. Synth.* **2006**, 83, 141.
18. Cockburn, W. F.; Marion, L., *Canadian J. Chem.* **1952**, 30, 92.
19. Herzig, J.; H., M., *Berichten der Deutschen Chemischen Gesellschaft* **1894**, 27, 319.
20. Hirschhauser, C.; Haseler, C. A.; Gallagher, T., *Angew. Chem. Int. Ed.* **2011**, 50, 5162.
21. Botuha, C.; Galley, C. M. S.; Gallagher, T., *Org. Biomol. Chem.* **2004**, 2, 1825.
22. Donets, P. A.; Cramer, N., *Angew. Chem. Int. Ed.* **2015**, 54, 633.
23. Guanti, G.; Riva, R., *Tet. Lett.* **2003**, 44, 357.
24. Honda, T.; Takahashi, R.; Namiki, H., *J. Org. Chem.* **2005**, 70, 499.
25. Figerio, F.; Haseler, C. A.; Gallagher, T., *Synlett* **2010**, 729.
26. Moss, R. A.; Terpinski, J.; Cox, D. D.; Denney, D. Z.; Krogh-Jespersen, K., *J. Am. Chem. Soc.* **1985**, 107, 2743.
27. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M., *Tet. Lett.* **1998**, 30, 5709.
28. Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K., *Org. Lett.* **2006**, 8, 963.
29. (a) Wattansin, S.; Do, H. D.; Bhongle, N.; Kathawala, F. G., *J. Org. Chem.* **1993**, 58, 1610; (b) Burgos, A.; Duffin, G. R.; Ellanes, G. J.; Wedge, K. J., *Journal of Labelled Compounds and Pharmaceuticals* **1996**, 38, 193.
30. Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H., *J. Am. Chem. Soc.* **1990**, 112, 7422.
31. Maruoka, K.; Concepcion, A. B.; Murase, N.; Oishi, M.; Hirayama, N.; Yamamoto, H., *J. Am. Chem. Soc.* **1993**, 115, 3943.
32. Nguyen, T.; Wicki, M. A.; Snieckus, V., *J. Org. Chem.* **2004**, 69, 7816.
33. Yamaguchi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H., *J. Org. Chem.* **1993**, 58, 1136.

34. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A., *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.
35. Krasovskij, A.; Knochel, P., *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
36. Struk, L.; Sosnicki, J. G., *Synthesis* **2012**, *44*, 735.
37. Chau, N. T. T.; Meyer, M.; Komagawa, S.; Chevallier, F.; Fort, Y.; Uchiyama, M.; Mongin, F.; Gros, P. C., *Chem. Eur. J.* **2010**, *16*, 12425.
38. Choppin, S.; Gros, P.; Fort, Y., *Org. Lett.* **2000**, *2*, 803.
39. Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P., *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
40. Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.* **1965**, *87*, 1353.
41. (a) Ivachtchenko, A. V.; Mitkin, O. D.; Tkachenko, S. E.; Okun, I. M.; Kysil, V. M., *Eur. J. Med. Chem.* **2010**, *45*, 782; (b) Han, X.; Civiello, R. L.; Mercer, S. E.; Macor, J. E.; Dubowchik, G. M., *Tetrahedron* **2009**, *50*, 386.
42. Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P., *J. Am. Chem. Soc.* **2011**, *133*, 9716.
43. Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T., *Org. Lett.* **2012**, *14*, 2250.
44. Nguyen, G.; Kourist, R.; Paravidino, M.; Hummel, A.; Redhorf, J.; Orru, R. V. A.; Hanefeld, U.; Bornscheuer, U. T., *Eur. J. Org. Chem.* **2010**, *14*, 2753.
45. (a) Marvel, C. S.; Brace, N. O., *J. Am. Chem. Soc.* **1949**, *71*, 37; (b) Poly, W.; Schomburg, D.; Hoffmann, H. M. R., *J. Org. Chem.* **1998**, *53*, 3701; (c) Bates, R. W.; Pinsa, A.; Kan, X., *Tetrahedron* **2010**, *66*, 6340.
46. (a) Barton, D. H. R.; Bashirdes, G.; Fourrey, J., *Tet. Lett.* **1983**, *24*, 1605; (b) Barton, D. H. R.; Bashirdes, G.; Fourrey, J., *Tetrahedron* **1988**, *44*, 147; (c) Barton, D. H. R.; O'Brien, R. E.; Strnhell, S., *J. Chem. Soc.* **1962**, 470.
47. Barbazan, P.; Carballo, R.; Covelo, B.; Loderio, C.; Lima, J. C.; Vazquez-Lopez, E. M., *Eur. J. Inorg. Chem.* **2008**, 2713.

48. McIntosh, J. M.; Goodbrand, H. B.; Masse, G. M., *J. Org. Chem.* **1974**, *69*, 202.
49. Harrington, P. J.; DiFiore, K. A., *Tet. Lett.* **1987**, *28*, 495.
50. (a) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D., *J. Org. Chem.* **1993**, *58*, 6952; (b) McDonald, F. E.; Zhu, H. Y. H., *J. Am. Chem. Soc.* **1998**, *120*, 4246.
51. McDonald, F. E.; Chatterjee, A. K., *Tet. Lett.* **1997**, *38*, 7687.
52. Weibel, J.; Blanc, A.; Pale, P., *Chem. Rev.* **2008**, *108*, 3149.
53. Dorel, R.; Echavarren, A. M., *Chem. Rev.* **2015**, *115*, 9028.
54. Firth, J. D.; O'Brian, P.; Ferris, L., *Org. Biomol. Chem.* **2014**, *12*, 9357.
55. Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H., *Tet. Lett.* **2007**, *48*, 8976.
56. Chen, J. L.; Namirembe, S.; Lauchert, L. T.; Tsougranis, G. H.; Isaacs, A. K., *Tet. Lett.* **2015**, *56*, 4105.
57. Matthews, S. L.; Heinekey, D. M., *J. Am. Chem. Soc.* **2006**, *128*, 2615.
58. Soderquist, J. A.; Anderson, C. L., *Tet. Lett.* **1986**, *27*, 3961.
59. Seregin, I. V.; Schammel, A. W.; Gevorgyan, V., *Tetrahedron* **2008**, *64*, 6876.
60. Boonsombat, J. Thesis (MSc).Thesis, Chulalongkorn University, Bangkok, 2001.
61. Caprio, V.; Mann, J., *J. Chem. Soc. Perkin 1* **1998**, 3151.
62. (a) Baldwin, J. E., *J. Chem. Soc. Chem. Comm.* **1976**, 734; (b) Baldwin, J. E.; Kruse, L. I., *J. Chem. Soc. Chem. Comm.* **1977**, 233; (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L., *J. Org. Chem.* **1977**, *42*, 3846.
63. Bates, R.; Song, P., *Tetrahedron* **2007**, *63*, 4497.
64. Bates, R. W.; Lek, T. G., *Synthesis* **2014**, *46*, 1731.
65. Bates, R. W.; Wang, K.; Zhou, G.; Kang, D. Z., *Synlett* **2015**, *26*, 751.
66. Bates, R. W.; Song, P., *Synthesis* **2010**, 2935.

67. (a) Bates, R. W.; Li, L.; Palani, K.; Phetsang, W.; Loh, J. K., *Asian J. Org. Chem.* **2014**, 3, 792; (b) Bates, R. W.; Palani, K., *Tet. Lett.* **2008**, 49, 2832.
68. Hili, F.; White, J. F.; Rizzacasa, M. A., *Org. Lett.* **2004**, 6, 1289.
69. Lim, J.; Kim, G., *Tet. Lett.* **2008**, 49, 88.
70. Pandey, G.; Balakrishnan, M.; Swaroop, P. S., *E. J. Org. Chem.* **2008**, 5839.
71. Toya, H.; Okano, K.; Takasu, K.; Ihara, M.; Takahashi, A.; Tanaka, H.; Tokuyama, H., *Org. Lett.* **2010**, 12, 5196.
72. Liu, S.; Hsu, H.; Chang, C.; Tsai, H. G.; Hou, D., *Eur. J. Org. Chem.* **2010**, 4771.
73. Fustero, S.; Moscardo, J.; Sanchez-Rosello, M.; Flores, S.; Guerola, M.; del Pozo, C., *Tetrahedron* **2001**, 67, 7417.
74. Kalyva, M.; Zografos, A. L.; Kapourani, E.; Giambazolias, L. D.; Papakyriakou, A.; Dive, V.; Lazarou, Y. G.; Georgiadis, D., *Chem. Eur J.* **2015**, 21, 3278.
75. Molander, G. A.; Ronn, M., *J. Org. Chem.* **1999**, 64, 5183.
76. Ichikawa, J.; Lapointe, G.; Iwai, Y., *Chem. Comm.* **2007**, 2698.
77. Rosiak, A.; Hoenke, C.; Jens, C., *Eur. J. Org. Chem.* **2007**, 4376.
78. Kurosu, M.; Liu, M.; Kishi, Y., *J. Am. Chem. Soc.* **2004**, 126, 12248.
79. Pelletier, J. C.; Kincaid, S., *Tet. Lett.* **2000**, 41, 797.
80. (a) Deska, J.; Kazmaier, U., *Angew. Chem. Int. Ed.* **2007**, 46, 4570; (b) Nishiyama, T.; Esumi, T.; Iwabuchi, T.; Irie, H.; Hatakayama, S., *Tet. Lett.* **1998**, 39, 43.
81. Zimmermann, H. E., *J. Org. Chem.* **1955**, 20, 549.
82. Bates, R. W.; Boonsombat, J., *J. Chem. Soc. Perkin Trans. 1* **2001**, 654.
83. Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N., *Tet. Asym.* **2004**, 15, 3531.
84. Jafarpour, M.; Rezaeifard, A.; Tayebbeh, G., *Phosphorus, Sulfur, and Silicon and the Related Elements* **2011**, 186, 140.
85. Saroj, D.; Sujit, K. G.; Dipakaranjan, M., *J. Org. Chem.* **2009**, 74, 1598.

86. Fukuyama, T.; Jow, C.; Cheung, M., *Tet. Lett.* **1995**, 69, 6373.
87. Barrett, A. G. M.; Betts, M. J.; Fenwick, A., *J. Org. Chem.* **1985**, 50, 169.
88. Yip, S. F.; Cheung, H. Y.; Zhou, Z.; F.Y., K., *Org. Lett.* **2007**, 9, 3469.
89. Andersson, *et. al.*, **2013**, US8367676, 28.
90. Wroblewski, S.; Trzebiatowski, K.; Jedrzejewski, B.; Pierzak, M.; Gawinecki, R.; Paczkowski, J., *J. Chem. Soc. Perkin 2* **1999**, 1909.
91. (a) Norrby, T.; Borje, A.; Lian, Z.; Bjorn, A., *Acta. Chem. Sc.* **1998**, 52, 77; (b) Fuji, T.; Yoshifuji, S.; Michishita, K.; Mitsukuchi, M.; Yoshida, K., *Chem. Pharm. Bull.* **1973**, 21, 2965.
92. Ouchi, H.; Asahina, A.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T., *Org. Lett.* **2014**, 16, 1980.
93. Benzt, S.; Notzli, S.; Siegel, J. S.; Eberli, D.; Jessen, H. J., *J. Med. Chem.* **2013**, 56, 10171.
94. Honraedt, A.; Gallagher, T., *Synlett* **2016**, 27, 67.
95. (a) Joubert, N.; Pohl, R.; Klepetarova, B.; Hocek, M., *J. Org. Chem.* **2007**, 72, 6797; (b) Stefko, M.; Hocek, M., *Synthesis* **2010**, 4199.
96. Dakin, H. D., *Am. Chem. J.* **1909**, 42, 477.
97. Voisin, A. S.; Bouillon, A.; Lancelot, J.; Rault, S., *Tetrahedron* **2005**, 61, 1417.
98. Ashfield, L.; Barnard, C. F. J., *Org. Proc. Res. Dev.* **2007**, 11, 39.
99. Lee, Y.; Kelly, M. J., *Tet. Lett.* **2006**, 47, 4897.
100. Taiga, Y.; Yohei, U.; Yoshiki, S.; Shinji, T.; Haruka, N.; Hayato, T.; Kazuhiko, S.; Kazushi, M., *Angew. Chem. Intl. Ed.* **2015**, 127, 14645.
101. Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L., *J. Org. Chem.* **1997**, 62, 2823.
102. Walter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L., *Org. Lett.* **2002**, 4, 973.

103. Bates, R. W.; Aslam, F. M.; Tang, C. H.; Simon, O., *Tetrahedron* **2014**, 70, 2134.
104. Baringhaus, K.; Matter, H.; Kurz, M., *J. Org. Chem.* **2000**, 65, 5031.
105. Kim, H. S.; Hong, M.; Lee, S.; Lee, H.; Suh, Y.; Oh, D.; Seo, J. H.; Choi, H.; Kim, J. Y.; Kim, K.; Kim, J. M.; Kim, J.; Kim, Y.; Park, S.; Park, H.; Lee, J., *Eur. J. Med. Chem.* **2015**, 104, 157.
106. Evans, D. A.; Ennis, M. D.; Mathre, D. J., *J. Am. Chem. Soc.* **1982**, 104, 1737.
107. Evans, D. A.; Weber, A. E., *J. Am. Chem. Soc.* **1986**, 108, 6757.
108. Basha, A.; Lipton, M.; Weinreb, S. M., *Tet. Lett.* **1977**, 48, 4171.
109. Liu, X.; Chen, H.; Yang, Y.; Wu, Y.; You, J., *Eur. J. Org. Chem.* **2014**, 3451.
110. Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S., *J. Am. Chem. Soc.* **1995**, 117, 3448.
111. Shvartsbart, A.; Smith, A. B. I., *J. Am. Chem. Soc.* **2014**, 136, 870.
112. Nicolaou, K. C.; Aversa, R. J.; Jin, J.; Rivas, F., *J. Am. Chem. Soc.* **2010**, 132, 6855.
113. Dale, J. A.; Dull, D. L.; Mosher, H. L., *J. Org. Chem.* **1969**, 34, 2543.
114. Marriere, E.; Rouden, J.; Tadino, V.; Lasne, M., *Org. Lett.* **2000**, 2, 1121.